Some other ELBS Low-priced Editions

Alstead, S., Macgregor, A. G. and Girdwood, R. H. TEXTBOOK OF MEDICAL TREATMENT	*Churchill Livingstone*
Baron, D. N. SHORT TEXTBOOK OF CHEMICAL PATHOLOGY	*English Universities Press*
Bell, G. H., Davidson, J. N. and Scarborough, H. TEXTBOOK OF PHYSIOLOGY AND BIOCHEMISTRY	*Churchill Livingstone*
Burgen, A. S. V. and Mitchell, J. F. GADDUM'S PHARMACOLOGY	*Oxford University Press*
Cruickshank, R., Duguid, J. P. and Swain, R. H. A. MEDICAL MICROBIOLOGY	*Churchill Livingstone*
Davey, T. H. and Wilson, T. DAVEY AND LIGHTBODY'S CONTROL OF DISEASE IN THE TROPICS	*H. K. Lewis*
Davidson, Sir S., Passmore, A. and Brock, J. F. HUMAN NUTRITION AND DIETETICS	*Churchill Livingstone*
Gray, C. H. CLINICAL CHEMICAL PATHOLOGY	*Arnold*
Gresham, G. A. and Jennings, A. R. AN INTRODUCTION TO COMPARATIVE PATHOLOGY	*Academic Press*
Havard, C. W. H. CURRENT MEDICAL TREATMENT	*Crosby Lockwood Staples*
Houston, J. C., Joiner, C. L. and Trounce, J. R. A SHORT TEXTBOOK OF MEDICINE	*English Universities Press*
Keele, C. A. and Neil, E. SAMSON WRIGHT'S APPLIED PHYSIOLOGY	*Oxford University Press*
Last, R. J. ANATOMY: REGIONAL AND APPLIED	*Churchill Livingstone*
Lawrence, D. R. CLINICAL PHARMACOLOGY	*Churchill Livingstone*
Maegraith, B. G. CLINICAL TROPICAL DISEASES	*Blackwell Scientific*
Manson-Bahr, Sir P. MANSON'S TROPICAL DISEASES	*Baillière Tindall*
Mollison, P. L. BLOOD TRANSFUSION IN CLINICAL MEDICINE	*Blackwell Scientific*
Romanes, G. J. CUNNINGHAM'S MANUAL OF PRACTICAL ANATOMY, Vols. I/III	*Oxford University Press*
Scott, Sir R. B. PRICE'S TEXTBOOK OF THE PRACTICE OF MEDICINE	*Oxford University Press*
Wilson, A. and Schild, H. O. APPLIED PHARMACOLOGY	*Churchill Livingstone*

The Editor

JOHN MACLEOD
M.B., Ch.B., F.R.C.P.Edin.

Consultant Physician, Western General Hospital, Edinburgh
Consultant Physician, Royal Edinburgh Hospital
Consultant Physician, Clinic for Rheumatic Diseases, Royal Infirmary, Edinburgh
Head of University Department of Medicine, Western General Hospital, Edinburgh

The Contributors

Past and Present Members of the Staff of
The Departments of Medicine,
University of Edinburgh
and Associated Clinical Units

DAVIDSON'S PRINCIPLES AND PRACTICE OF MEDICINE

A TEXTBOOK FOR STUDENTS AND DOCTORS

EDITED BY

John Macleod

Eleventh Edition

THE ENGLISH LANGUAGE BOOK SOCIETY
and
CHURCHILL LIVINGSTONE
1974

Churchill Livingstone
Medical Division of Longman Group Limited
Represented in the United States of America by Longman Inc., New York, and by associated companies, branches and representatives throughout the world

© Longman Group Limited 1974

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, without the prior permission of the publishers
(Churchill Livingstone, 23 Ravelston Terrace, Edinburgh)

First Edition	1952
Reprinted	1953
Second Edition	1954
Reprinted	1955
Third Edition	1956
Reprinted	1957
Fourth Edition	1958
Reprinted	1959
Fifth Edition	1960
Reprinted	1961
Sixth Edition	1962
Reprinted	1963
Seventh Edition	1964
Reprinted	1965
First E.L.B.S. Edition published	1965
Eighth Edition	1966
Reprinted	1968
Second E.L.B.S. Edition published	1967
Third E.L.B.S. Edition published	1968
Ninth Edition	1968
Reprinted	1969
Reprinted	1970
Tenth Edition	1971
Reprinted	1972
Fourth E.L.B.S. Edition published	1971
Reprinted	1972
Reprinted	1972
Fifth E.L.B.S. Edition published	1973
Eleventh Edition	1974
Sixth E.L.B.S. Edition published	1974

ISBN 0 443 01232 6

Printed in Great Britain

Preface to the Eleventh Edition

Davidson's Principles and Practice of Medicine has now appeared in eleven editions and eighteen reprints since it was first published in 1952. The continuing success of this book is a remarkable tribute to the genius and vision of Sir Stanley Davidson. The general editorial policy he laid down initially has undoubtedly stood the test of time. A hazard now to be avoided is that a well-established textbook may tend to lose its vitality as years go by. Sir Stanley's belief was that momentum could be retained through firm editorial control and the regular recruitment of younger authors.

In the tenth edition it was decided to aim at having more than one contributor to each section. Two heads are better than one, especially when maturity and experience are combined with youth and enthusiasm; moreover, in the event of the retirement of one contributor, the other would provide continuity. It has now been agreed that senior authors, on giving up active practice, would cease to contribute and thus make way for younger colleagues. In pursuance of this policy, new co-authors have now been introduced to the sections on infection, nutrition, digestive disorders, liver diseases, endocrinology and diseases of the connective tissues; these areas particularly have been extensively rewritten. The remainder has also been thoroughly revised. We have succeeded in reducing the size of the book mainly by discarding material which has been superseded but have not hesitated to make room for accounts of important new advances. In this regard we are particularly grateful to students and doctors from many parts of the world who have provided us with the constant challenge of constructive criticism.

The order of presentation of the contents, altered in the tenth edition, has been substantially retained. The opening chapters deal with fundamental factors in disease, such as genetics, immunology, infection, nutrition and electrolyte balance. These are followed by accounts of diseases of the various systems and outlines of psychiatry and acute poisoning. Finally, there is a description of those tropical diseases which may be encountered in temperate climates.

From the beginning it was agreed that no attempt should be made to include every disease, but to devote most of the available space to those disorders commonly found in clinical practice. The selection of other material is based principally on its educational value. In addition, although diseases such as typhoid fever and rabies are rarities in Britain and the incidence of tuberculosis has markedly decreased, conditions such as these have been included since they are still of great importance in many other parts of the world and, nowadays, doctors must be aware of problems in communities other than their own.

The separate supplement dealing with tropical diseases, mainly written by Dr F. J. Wright and Lieutenant-General Sir James Baird, has continued to be very well received and has enjoyed large sales in Asia and Africa where it can also be purchased combined with the parent book, in a large paperback edition at a greatly reduced price, under the auspices of the English Language Book Society. There are translations into Spanish, Italian, Greek and Croato-serbian. Other advances into Europe are in progress, while the book continues to be widely read in the Commonwealth and the Americas. Production of the eleventh edition in limp covers and in large numbers has enabled the publishers to sell the book at a modest price despite continuing increases in costs at every stage.

Some of us have had the privilege of being associated with this textbook from the outset and are particularly aware of the responsibilities involved in its production. Our task has been made easier by the enjoyment of participation in a team, and we have kept in mind Sir Stanley's insistence that all writing must be easily comprehensible. In preparing the eleventh edition it has been our primary objective to ensure that the book continues to reflect the constantly evolving pattern of clinical practice. If we have been successful, we shall entertain the hope that 'Davidson' will contribute as much to the education of medical students, both undergraduate and postgraduate, in the future as it had done in the past.

JOHN MACLEOD.

Edinburgh, 1974

Acknowledgments

We have had generous help from many colleagues and we would like to express our thanks especially to Drs N. C. Allan, D. B. Horn, E. Housley, I. G. Walton and Mr C. Vaughan Ruckley. We are indebted to Professors Bruce Cruickshank and C. I. Phillips and to Dr G. A. McDonald for supplying the colour plates. Mr J. E. Pizer of the Medical Illustration Service of the University of Edinburgh prepared most of the new diagrams. Acknowledgment for the inclusion of others has been made in the text.

Miss E. A. J. Nelson gave us invaluable assistance in the preparation of the manuscript.

It is a special pleasure to acknowledge all the help we have had from our publishers and from Miss Mary Emmerson in particular. Their unique blend of expertise and patience has provided unfailing support.

List of Contributors

BAIRD, Sir JAMES, K.B.E., M.D., F.R.C.P.Edin., F.R.C.P.Lond.
Lieutenant-General, late R.A.M.C., Director-General of Army Medical Services. Formerly Professor of Military Medicine of the Royal Army Medical College and the Royal College of Physicians, London. Previously Officer-in-Charge, Medical Division, British Military Hospital, Singapore.
Tropical Diseases and Helminthic Infections.

BAIRD, JOYCE D., M.A., M.B., Ch.B.Aberd., M.R.C.P.Edin.
Lecturer, University Department of Medicine, Western General Hospital, Edinburgh.
Diabetes Mellitus.

CARSTAIRS, G. M., M.D., F.R.C.P.Edin., D.P.M.
Vice-Chancellor, University of York. Formerly Professor of Psychological Medicine, University of Edinburgh.
Psychiatry.

CREAN, GERARD P., Ph.D., F.R.C.P.Edin.
Hon. Lecturer in Medicine, University of Glasgow (Western Infirmary). Consultant Physician, Southern General Hospital, Glasgow. Physician-in-charge, The Gastrointestinal Centre, Southern General Hospital, Glasgow.
Diseases of the Digestive System.

DUTHIE, J. J. R., M.B., Ch.B., F.R.C.P.Edin.
Professor of Medicine (Rheumatology), University of Edinburgh. Hon. Consultant Physician, Northern General Hospital. Physician-in-charge, Rheumatic Diseases Unit, Northern General Hospital, Edinburgh.
Diseases of Connective Tissues, Joints and Bones.

EMERY, A. E. H., M.D., Ph.D., D.Sc., F.R.C.P.Edin.
Professor of Human Genetics (Western General Hospital), University of Edinburgh. Consultant in Medical Genetics, Lothian Health Board, Scotland.
Genetic Factors in Disease.

FRENCH, E. B., B.A., M.B., B.Chir.Cantab., F.R.C.P.Edin., F.R.C.P.Lond.
Reader, University Department of Medicine and Hon. Consultant Physician, Western General Hospital, Edinburgh.
Infection and Disease.

GEDDES, A. M., M.B., Ch.B., F.R.C.P.Edin.
Lecturer in Infectious Diseases, University of Birmingham. Consultant Physician, Department of Communicable and Tropical Diseases, East Birmingham Hospital, Birmingham.
Infection and Disease.

GIRDWOOD, R. H., M.D., Ph.D., F.R.C.P.Edin., F.R.C.P.Lond., F.R.C.Path.
Professor of Therapeutics, University of Edinburgh. Hon. Consultant Physician, Royal Infirmary, Edinburgh.
Disorders of the Blood and Blood-forming Organs.

GOULD, J. C., B.Sc., M.D., F.R.C.P.Edin., F.Inst.Biol., M.R.C.Path., F.R.S. Edin.
Director of the Central Microbiological Laboratories, Edinburgh.
Infection and Disease.

GRANT, I. W. B., M.B., Ch.B., F.R.C.P.Edin.
Consultant Physician, Respiratory Diseases Unit, Northern General Hospital, Edinburgh.
Diseases of the Respiratory System.

HORNE, N. W., M.B., Ch.B., F.R.C.P.Edin.
Hon. Senior Lecturer, Department of Respiratory Diseases and Tuberculosis, University of Edinburgh. Consultant Physician, Chest Unit, City Hospital, Edinburgh.
Diseases of the Respiratory System.

INNES, JAMES, M.D., F.R.C.P.Edin.
Senior Lecturer in Medicine, University of Edinburgh. Consultant Physician, Royal Infirmary, Edinburgh.
Disorders of the Blood and Blood-forming Organs.

IRVINE, W. J., D.Sc., M.B., Ch.B., F.R.C.P.E., M.R.C.Path.
Reader, Department of Therapeutics, University of Edinburgh. Consultant Physician and Physician-in-charge, Department of Endocrinology, Royal Infirmary, Edinburgh. Head of Immunology Laboratories, 2 Forrest Road, Edinburgh.
Immunological Factors in Disease.
Diseases of the Endocrine System.

JULIAN, D. G., M.A., M.D., F.R.C.P.Edin., F.R.C.P.Lond., F.R.A.C.P.
Senior Lecturer in Medicine, University of Edinburgh. Consultant Physician, Royal Infirmary, Edinburgh.
Diseases of the Cardiovascular System.

LAWSON, A. A. H., M.D., F.R.C.P.Edin.
Consultant Physician, West Fife Group of Hospitals.
Acute Poisoning.

MCCORMICK, J. N., M.B., Ch.B., M.R.C.P.Edin.
Hon. Senior Lecturer, Departments of Medicine and Bacteriology, University of Edinburgh. Consultant Physician, Rheumatic Diseases Unit, Northern General Hospital, Edinburgh.
Diseases of Connective Tissues, Joints and Bones.

McHardy, G. J. R., M.A., B.Sc., B.M., F.R.C.P.Edin., F.R.C.P.Lond.
Senior Lecturer, Department of Respiratory Diseases and Tuberculosis, University of Edinburgh. Consultant Physician, Chest Unit, City Hospital, Edinburgh. Consultant Clinical Respiratory Physiologist, City Hospital and Western General Hospital, Edinburgh.
Diseases of the Respiratory System.

McManus, J. P. A., M.B., Ch.B., F.R.C.P.Edin.
Professor of Medicine and Director of Gastroenterology, University of Laval, Quebec, Canada. Formerly Senior Lecturer, Department of Medicine, and Consultant Physician, Gastrointestinal Unit, Western General Hospital, Edinburgh.
Diseases of the Liver and Biliary Tract.

Matthew, Henry, M.D., F.R.C.P.Edin.
Senior Lecturer, Department of Therapeutics, University of Edinburgh. Consultant Physician, Royal Infirmary, Edinburgh. Physician-in-charge, Area Poisoning Treatment Centre, Royal Infirmary, Edinburgh. Director, Scottish Poisons Information Bureau.
Acute Poisoning.

Mawdsley, C., M.D., F.R.C.P.Edin., F.R.C.P.Lond.
Senior Lecturer in Medical Neurology, University of Edinburgh. Hon. Consultant Neurologist, Royal Infirmary and Northern General Hospital, Edinburgh.
Diseases of the Nervous System.

Richmond, John, M.D., F.R.C.P.Edin., F.R.C.P.Lond.
Professor of Medicine, University of Sheffield. Hon. Consultant Physician, Sheffield Area Health Authority (Teaching).
Genetic Factors in Disease.
Diseases of the Liver and Biliary Tract.

Robson, J. S., M.D., F.R.C.P.Edin.
Reader in Medicine, University of Edinburgh. Hon. Consultant Physician, Royal Infirmary, Edinburgh.
Disturbances in Water and Electrolyte Balance and in Hydrogen Ion Concentration.
Diseases of the Liver and Biliary Tract.
Diseases of the Kidney and Urinary System.

Shearman, D. J. C., Ph.D., M.B., Ch.B., F.R.C.P.Edin.
Senior Lecturer, Department of Therapeutics, University of Edinburgh. Hon. Consultant Physician, Royal Infirmary, Edinburgh.
Diseases of the Digestive System.

SIMPSON, J. A., M.D.Glasg., F.R.C.P.Edin., F.R.C.P.Lond., F.R.C.P.Glasg., F.R.S.Edin.
Professor of Neurology, University of Glasgow. Senior Neurologist, Institute of Neurological Sciences, Southern General Hospital and Consultant Neurologist, Western Infirmary, Glasgow.
Diseases of the Nervous System.

SMALL, W. P., V.R.D., M.B., Ch.B., Ch.M., F.R.C.S.Edin., F.R.C.P.Edin.
Consultant Surgeon, Western General Hospital, Edinburgh.
Diseases of the Digestive System.

STRONG, J. A., M.B.E., M.A., M.D.Dubl., F.R.C.P.Edin., F.R.C.P.Lond., F.R.S.Edin.
Professor of Medicine (Western General Hospital), University of Edinburgh. Hon. Consultant Physician, Western General Hospital, Edinburgh. Hon. Consultant Physician, Medical Research Council Clinical and Population Cytogenetics Research Unit.
Diseases of the Endocrine System, including Diabetes Mellitus. Obesity.

TRUSWELL, A. S., M.D., M.R.C.P.Lond., M.F.C.M.
Professor of Nutrition and Dietetics, Queen Elizabeth College, University of London. Hon. Consultant Physician in Nutrition, Charing Cross Hospital Medical School, London.
Nutritional Factors in Disease.

TURNER, R. W. D., O.B.E., M.A., M.D.Cantab., F.R.C.P.Edin., F.R.C.P.Lond.
Reader, University Department of Medicine and Hon. Consultant Physician, Western General Hospital, Edinburgh.
Diseases of the Cardiovascular System.

WALTON, H. J., Ph.D., M.D., F.R.C.P.Edin., D.P.M.
Professor of Psychiatry, University of Edinburgh. Director, University Department of Psychiatry, Western General Hospital. Hon. Consultant Psychiatrist, Royal Edinburgh Hospital.
Psychiatry.

WRIGHT, F. J., M.A., M.D.Cantab., F.R.C.P.Edin., F.R.C.P.Lond., D.T.M. & H. Eng.
Head of Medical Department, Kilmanjaro Christian Medical Centre, Moshi, Tanzania. Hon. Senior Lecturer in Medicine, University of Dar es Salaam, Tanzania. Formerly Senior Lecturer in Diseases of Tropical Climates, University of Edinburgh. Previously Government Medical Specialist, Kenya.
Nutritional Factors in Disease.
Tropical Diseases and Helminthic Infections.

Contents

GENETIC FACTORS IN DISEASE 1

IMMUNOLOGICAL FACTORS IN DISEASE 15
- Components of the Immune System 16
- Mechanism of the Immune Response 20
- Immuno-deficiency and Lympho-proliferative Disorders 25
- Types of Immune Reaction and their Relation to Human Disease 28
- Suppression of Immune Reactions or of their Effects 39

INFECTION AND DISEASE 43
- Nature of the Micro-organism 43
- Epidemiology and Spread of Infection 45
- Defence of the Human Host 49
- Clinical Features of Infection 51
- Diagnosis of Infectious Disease 52
  - Pyrexia of Unknown Origin 54
- Treatment of Infections 56
- Prevention of Infection 57
  - Active and Passive Immunisation 58
- Infectious Diseases 60
  - Streptococcal Infections 61
  - Staphylococcal Infections 63
  - Whooping-cough 64
  - Diphtheria 65
  - Typhoid and Paratyphoid Fevers 69
  - Bacterial Food Poisoning 71
  - Bacillary Dysentery 74
  - Tetanus 76
  - Brucellosis 78
  - Gonorrhoea 79
  - Syphilis 80
  - Leptospirosis 82
  - Measles 84
  - Rubella 86
  - Mumps 87
  - Chickenpox 88
  - Smallpox 89
- Chemotherapy of Infections 93
  - Sulphonamides 94
  - Antibiotics 95
  - Miscellaneous Chemotherapy 104
  - Selection of Antimicrobial Agent 105

NUTRITIONAL FACTORS IN DISEASE 111

- Quantitative Aspects 113
- Qualitative Aspects 116
- Protein-Calorie Malnutrition 117
  - Kwashiorkor 118
  - Nutritional Marasmus 123
- Nutritional Dwarfing and Mild to Moderate PCM 125
- Water and Electrolytes 126
- Minerals 126
- Vitamins and Disorders due to Vitamin Deficiency 130
  - Vitamin A 132
  - Vitamin D 135
  - Vitamin K 148
  - Vitamin C—Ascorbic Acid 148
  - Vitamin B Complex 152
    - Thiamin 152
    - Niacin 158
    - Riboflavin 162
    - Pyridoxine 163
    - Vitamin B_{12} 164
    - Folate 165
- Nutritional Anaemias 165
- Nutritional Neurological Syndromes 166
- Nutritional Disorders of Skin, Hair, Nails, Mouth and Eyes 170
- Biochemical Diagnosis and Subclinical Vitamin Deficiencies 170
- Prevention of Nutritional Deficiencies 172
- Obesity 172

DISTURBANCES IN WATER AND ELECTROLYTE BALANCE AND IN HYDROGEN ION CONCENTRATION 185

- Sodium Depletion 186
- Primary Water Depletion 188
- Potassium Depletion and Excess 189
- Magnesium Deficiency and Intoxication 193
- Water Intoxication 193
- Sodium and Water Accumulation 194
- Disturbances in Hydrogen Ion Concentration 200

DISEASES OF THE CARDIOVASCULAR SYSTEM 206

- Physical Examination 206
- Electrocardiography 214
- Other Investigative Procedures 223
- Disorders of Cardiac Rhythm and Conduction 225
  - Sinus Rhythms 226
  - Ectopic Rhythms 227
    - Anti-arrythmic Drugs 233
  - Heart Block 235

  - Cardiac Arrest 239
  - Syncope 241
- Cardiac Failure 242
  - Left-sided Cardiac Failure 244
  - Right-sided Cardiac Failure 246
  - Treatment of Cardiac Failure 247
- Acute Circulatory Failure 251
  - Acute Cardiac Failure 251
  - Peripheral Circulatory Failure 251
- Diseases of the Heart Valves 253
  - Mitral Valve Disease 253
  - Aortic Valve Disease 256
  - Pulmonary Valve Disease 258
  - Tricuspid Valve Disease 258
- Rheumatic Fever 259
- Infective Endocarditis 263
- Ischaemic Heart Disease 265
  - Angina Pectoris 268
  - Myocardial Infarction 269
- Hypertension 273
- Pulmonary Factors in Heart Disease 281
  - Pulmonary Arterial Hypertension 281
  - Pulmonary Embolism and Infarction 282
  - Pulmonary Heart Disease 284
- Diseases of the Myocardium 285
  - Acute Myocarditis 285
  - Chronic Cardiomyopathies 286
- Diseases of the Pericardium 287
  - Acute Pericarditis 287
  - Chronic Constrictive Pericarditis 289
- Congenital Heart Disease 290
  - Patent Ductus Arteriosus 291
  - Coarctation of the Aorta 292
  - Atrial Septal Defect 293
  - Ventricular Septal Defect 294
  - Pulmonary Stenosis 294
- Surgical Treatment of Heart Disease 296
- Heart Disease in Pregnancy 297
- Cardiac Neurosis 298
- Diseases of Arteries 299
  - Arteriosclerosis 299
  - Atherosclerosis 300
    - Atherosclerosis obliterans 300
    - Sudden Occlusion of a Major Artery 303
    - Atherosclerosis and Aneurysm Formation 303
  - Dissecting Aneurysm of Aorta 303
  - Inflammatory Arterial Disease 304
    - Syphilitic Aortitis 304

        Thrombo-angiitis Obliterans 305
        Polyarteritis 305
        Cranial Arteritis 306
        Takayashu's Syndrome 306
    Raynaud's Phenomenon 306
Diseases of Veins 307
    Venous Thrombosis 307
Prevention of Cardiovascular Disease 310

DISEASES OF THE RESPIRATORY SYSTEM 312
- Anatomy 312
- Physiology 316
- Common Manifestations of Respiratory Disease 320
- Investigation of Respiratory Disease 324
- Treatment of Respiratory Disease 329
- Infections of the Respiratory Tract 334
  - Acute Coryza 335
  - Pharyngo-conjunctival Fever 336
  - Acute Laryngo-tracheo-bronchitis 336
  - Influenza 338
  - Acute Catarrhal Laryngitis 339
  - Acute Bronchitis 339
  - The Pneumonias 341
  - Tuberculosis 354
    - Primary Pulmonary Tuberculosis 359
    - Acute Miliary Tuberculosis 361
    - Post-primary Pulmonary Tuberculosis 362
    - Treatment of Tuberculosis 366
    - Prevention of Tuberculosis 370
  - Respiratory Diseases Caused by Fungi 372
- Allergic Diseases of the Respiratory Tract 373
  - Allergic Rhinitis 374
  - Bronchial Asthma 375
  - Pulmonary Eosinophilia 381
  - Allergic Alveolitis 382
- Diseases of the Larynx 383
  - Chronic Laryngitis 383
  - Laryngeal Paralysis 384
  - Laryngeal Obstruction 385
- Disorders of the Trachea 386
- Chronic Bronchitis and Emphysema 387
- Bronchiectasis 393
- Bronchial Obstruction and Its Consequences 396
  - Hyaline Membrane Disease 401
- Intrathoracic Tumours 401
  - Bronchial Carcinoma 401
  - Bronchial Adenoma 404
  - Secondary Tumours of the Lung 405

- Tumours of the Mediastinum 405
- Interstitial Lung Disease 407
  - Fibrosing Alveolitis 407
  - Idiopathic Pulmonary Haemosiderosis 408
- Pulmonary Fibrosis 408
- Sarcoidosis 409
- Occupational Lung Diseases 410
  - Diseases Caused by Mineral Dusts (Pneumoconiosis) 410
  - Diseases Caused by Organic Dusts 413
- Diseases of the Pleura 414
  - Pleural Effusion 414
  - Empyema Thoracis 418
  - Spontaneous Pneumothorax 421
- Deformities of the Chest Wall 425
- Prevention of Respiratory Disease 425

DISEASES OF THE DIGESTIVE SYSTEM 428

- Functions of the Gastrointestinal Tract 428
- Symptoms of Gastrointestinal Disease 432
- Examination of the Abdomen 436
- Investigation of the Gastrointestinal Tract 436
  - Radiology 436
  - Endoscopy 439
  - Biopsy and Cytology 440
  - Secretory Studies 441
  - Motility and Bacteriological Studies 442
  - Examination of the Stool 443
- Diseases of the Mouth 443
  - The Teeth 443
  - Stomatitis 444
  - The Tongue 446
  - The Salivary Glands 446
- Diseases of the Oesophagus 447
  - Dysphagia 448
  - Oesophageal Hiatus Hernia and Reflux Oesophagitis 449
  - Traction Diverticulum 452
  - Pharyngeal Pouch 452
  - Achalasia of the Cardia 452
  - Diffuse Spasm of the Oesophagus 454
  - Carcinoma of the Oesophagus 454
- Diseases of the Stomach and Duodenum 455
  - Peptic Ulcer 455
  - Gastroduodenal Haemorrhage 464
  - Acute Perforation of a Peptic Ulcer 464
  - Gastric Outlet (Pyloric) Obstruction 468
  - Zollinger Ellison Syndrome 470
  - Complications following Operations on the Stomach 470
  - Gastritis 474

- Carcinoma of the Stomach 476
- Diseases of the Pancreas 480
  - Anatomy and Physiology 480
  - Investigation of the Pancreas 480
  - Acute Pancreatitis 481
  - Chronic Pancreatitis 484
  - Pancreatic Cysts 486
  - Tumours of the Pancreas 486
- Diseases of the Small Intestine 488
  - Malabsorption 488
  - Crohn's Disease 496
  - The Acute Abdomen 500
  - Intestinal Obstruction 501
  - Peritonitis 504
  - Acute Appendicitis 506
  - Tumours of the Small Intestine 507
- Diseases of the Large Intestine 508
  - Anatomy and Physiology 508
  - Physical Examination 508
  - Ulcerative Colitis 508
  - Diverticular Disease 515
  - Carcinoma of the Colon and Rectum 517
  - Benign Tumours of the Large Intestine 519
  - Multiple Polyposis 520
  - Megacolon 520
- Infections of the Alimentary Tract 521
- Vascular Disorders of the Alimentary Tract 521
- Psychogenic Disorders of the Digestive System 522
- Prevention of Diseases of the Digestive System 527

DISEASES OF THE LIVER AND BILIARY TRACT 529
- Anatomical Considerations 529
- Metabolic Activities of the Liver 530
- Liver Function Tests 533
- Jaundice 538
  - Haemolytic, Hepatocellular and Obstructive Jaundice 539
  - Congenital Non-haemolytic Hyperbilirubinaemias 541
  - Effect of Drugs on Bilirubin Metabolism 543
- Acute Parenchymal Disease of the Liver 544
  - Viral Hepatitis 545
    - Acute Infective Hepatitis 546
    - Serum Hepatitis 548
  - Acute Massive Liver Necrosis 549
- Chronic Parenchymal Disease 554
  - Chronic Hepatitis 557
  - Cirrhosis of the Liver 558
  - Other Diseases Involving Hepatic Fibrosis 566
- New Growths of the Liver 568

- Diseases of the Gall-bladder and Bile Ducts 568
  - Anatomy and Physiology 568
  - Evaluation of Gall-bladder Structure and Function 569
  - Acute Cholecystitis 570
  - Chronic Cholecystitis 572
  - Cholelithiasis 572
  - Biliary Dyskinesia 576
  - Tumours of the Gall-bladder and Bile Ducts 576
- Prevention of Diseases of the Liver and Biliary Tract 577

DISEASES OF THE KIDNEY AND URINARY SYSTEM 579

- Structure and Mode of Action of the Kidneys 579
- Diagnosis of Renal Disease 583
- Glomerulonephritis 589
  - Proliferative Glomerulonephritis 589
  - Minimal Lesion and Membranous Glomerulonephritis 594
  - Chronic Glomerulonephritis 597
- Infections of the Urinary Tract 601
  - Acute Pyelonephritis 601
  - Chronic Pyelonephritis 603
  - Cystitis, Urethritis and Prostatitis 605
  - Renal Tuberculosis 606
- Renal Failure 607
- Obstruction of the Urinary Tract 612
- Renal and Vesical Calculi and Nephrocalcinosis 613
- Renal Hypertension and Unilateral Renal Disease 616
- Polycystic Disease of the Kidneys 617
- Tumours of Kidney and Urinary Tract 617
- Benign Enlargement of the Prostate Gland 619
- Prevention of Diseases of the Kidney and the Urinary Tract 619

DISEASES OF THE ENDOCRINE SYSTEM 621

- The Hypothalamus and the Pituitary Gland 622
  - Anatomy and Physiology 622
  - Diagnosis of Disordered Pituitary Function 623
  - Clinical Manifestations of Pituitary Disease 624
  - Tumours of the Pituitary Gland 624
  - Syndromes due to Anterior Pituitary Hypersecretion 626
  - Syndromes due to Anterior Pituitary Hyposecretion 626
  - Diabetes Insipidus 629
- The Thyroid Gland 631
  - Anatomy and Physiology 631
  - Hyperthyroidism 631
    - Exophthalmos 641
  - Hypothyroidism 642
  - Goitre 645
    - Hashimoto's Thyroiditis 645
    - Subacute (de Quervain's) Thyroiditis 646

- Dyshormonogenesis 646
- Carcinoma of the Thyroid Gland 646
- Simple Goitre 647
- Calcitonin 648
- The Parathyroid Glands 648
  - Hyperparathyroidism 649
  - Hypoparathyroidism 651
    - Tetany 652
- The Adrenal Glands 654
  - Anatomy and Physiology 654
  - Hyperfunction of the Adrenal Gland 655
    - Cushing's Disease 656
    - Aldosteronism 659
  - Insufficiency of the Adrenal Cortex 659
    - Addison's Disease 660
    - Secondary Adrenal Insufficiency 662
    - Congenital Adrenal Insufficiency with Hyperplasia 663
    - Investigation of Adrenal Insufficiency 663
    - Treatment of Adrenal Insufficiency 666
  - Corticosteroids and ACTH in the Treatment of Disease 669
  - Phaeochromocytoma 671
- Sexual Disorders in the Male 672
  - Hypogonadism 672
  - Cryptorchism 673
  - Impotence 673
  - Infertility in the Male 674
- Disorders of Sexual Determination and Differentiation 674
- Disorders of the Menopause 674
- Diabetes Mellitus 675

DISEASES OF THE BLOOD AND BLOOD-FORMING ORGANS 713

- Blood Formation 713
- Blood Destruction 718
- Terms Relating to Blood Disorders 718
- Disorders of the Red Blood Cells 720
  - The Anaemias 720
    - Anaemia due to Deficiency of Iron 722
    - Anaemia due to Deficiency of B_{12} or Folate—the Megaloblastic Anaemias 727
    - Anaemia due to Deficiency of Vitamin C 733
    - Anaemia due to Deficiency of Thyroxine 734
    - Pancytopenia 734
    - Anaemias due to Excessive Blood Destruction (Haemolytic Anaemias) 735
    - Anaemias of Uncertain Origin 741
  - Erythrocytosis 742
  - Polycythaemia Vera 742

Disorders of the White Blood Cells and the Reticulo-endothelial System 744
  Agranulocytosis 744
  Infectious Mononucleosis 745
  The Leukaemias 747
  The Malignant Lymphomas (the Reticuloses) 753
    Lymphadenoma (Hodgkin's Disease) 753
  Myelomatosis 755
  Diseases of Lipoid Storage 756
  Hypersplenism 756
Haemorrhagic Disorders 756
  Vascular Purpuras 759
  Von Willebrand's Disease 760
  Hereditary Haemorrhagic Telangiectasia 760
  Thrombocytopenic Purpura 761
  Haemophilia 762
  Christmas Disease 764
  Hypoprothrombinaemia 764
  Congenital or Acquired Fibrinogenopenia 765
Thrombocytosis 766
Prevention of Disorders of the Blood 766

DISEASES OF CONNECTIVE TISSUES, JOINTS AND BONES 768
Rheumatoid Arthritis 768
Ankylosing Spondylitis 779
Systemic Lupus Erythematosus 780
Dermatomyositis 781
Scleroderma 782
Polymyalgia Rheumatica 782
Gout 783
Pseudo-Gout (Chondrocalcinosis) 786
Osteoarthrosis 786
Miscellaneous Lesions of Connective Tissue 788
Diseases of Bone 790
  Metabolic and Endocrine Diseases 790
  Infections 790
  Tumours 790
  Paget's Disease 791
Prevention of Diseases of Connective Tissue, Joints and Bones 791

DISEASES OF THE NERVOUS SYSTEM 793
Applied Anatomy and Physiology 793
  The Motor System 793
  The Sensory System 801
  The Reflexes 806
Localising Signs of Cerebral Disease 808
Disorders of the Cranial Nerves 813

Coma 825
The Epilepsies 827
Cerebral Tumours 832
Headache 838
Disorders of the Blood Vessels 841
  Cerebral Atherosclerosis 842
  Cerebral Arterial Thrombosis 844
  Cerebral Embolism 845
  Intracerebral Haemorrhage 846
  Cerebral Aneurysms 848
  Subarachnoid Haemorrhage 849
  Cerebral Venous Thrombosis 851
The Cerebrospinal Fluid 852
Infections of the Brain, Spinal Cord and Meninges 853
  Intracerebral Abscess 853
  Spinal Epidural Abscess 855
  Meningitis 855
    Meningococcal and Acute Pyogenic Meningitis 856
    Tuberculous Meningitis 857
    Viral Meningitis 859
  Neurosyphilis 860
  Viral Infections 863
    Slow Viral Infections 864
    Encephalitis 864
    Acute Anterior Poliomyelitis 867
    Herpes Zoster 868
Demyelinating Diseases 869
  Disseminated Sclerosis 869
  Acute Demyelinating Encephalomyelitis 872
Disorders of the Extrapyramidal System 873
  Parkinsonism 873
  Hepato-lenticular Degeneration 876
  Sydenham's Chorea 877
  Huntington's Chorea 878
  Athetosis 879
  Kernicterus 879
  Spasmodic Torticollis 880
Congenital and Degenerative Disorders 881
  Motor Neurone Disease 881
  The Hereditary Ataxias 884
  Syringomyelia 885
  Neurofibromatosis 886
Compression of the Spinal Cord or Nerve Roots 887
  Paraplegia 889
  Cervical Disc Herniation and Cervical Spondylosis 890
  The Lumbago-Sciatica Syndrome 892
Nutritional Neurological Syndromes 894
  Vitamin B_{12} Neuropathy 894

    - Wernicke's Encephalopathy 896
  - Neurological Complications of Carcinoma 897
  - Disorders of Peripheral Nerves 899
    - Mononeuropathy 899
    - Mononeuritis Multiplex 900
    - Localised Radiculopathy 900
    - Generalised Polyneuropathies 901
    - Myasthenia Gravis 904
  - Diseases of Muscle 906
    - Genetically Determined Myopathy 906
    - Congenital Myopathies 908
    - Metabolic Myopathies 908
    - Polymyositis 908
  - The Prevention of Diseases of the Nervous System 908

PSYCHIATRY 911

  - Classification 911
  - Examination and Formulation 913
  - The Psychoneuroses 918
    - Anxiety Neurosis 918
    - Hysterical Psychoneurosis 922
    - Obsessional Neurosis 926
  - Personality Disorders 927
    - Obsessional Personality 928
    - Schizoid Personality 929
    - Hysterical Personality 930
    - Sociopathy 930
  - Alcoholism and Drug Addiction 932
  - Sexual Deviation 934
  - Psychosomatic Disorders 935
  - Functional Psychoses 936
    - Depressive Illness 936
    - Schizophrenia 938
  - Organic Psychoses 939
    - Delirium 940
    - Dementia 941
  - Psychiatric Disorders in the Elderly 941
  - The Uses and Misuses of Psychotropic Drugs 942

ACUTE POISONING 947

  - Classification and Diagnosis 948
  - General Therapeutic Measures 950
  - Barbiturate Poisoning 953
  - Benzodiazepine Poisoning 956
  - Poisoning by Tricyclic Antidepressants 957
  - Salicylate Poisoning 957
  - Carbon Monoxide Poisoning 958
  - Acute Poisoning in Children 959
  - Industrial and Agricultural Poisoning 960

TROPICAL DISEASES AND HELMINTHIC INFECTIONS 961
- Historical Aspects 961
- Diagnosis 964
- Malaria 964
- Amoebic Dysentery 970
- Rabies 972
- Helminthic Infections 973
- Summary of other Tropical Diseases 974
- Summary of Common Tropical Helminths 976

DIETS 985

WEIGHT TABLES 1006

NOTES ON INTERNATIONAL SYSTEM OF UNITS (SI UNITS) 1008

BIOCHEMICAL AND HAEMATOLOGICAL VALUES 1009

NOMOGRAMS OF METRIC EQUIVALENTS 1012

INDEX 1013

Genetic Factors in Disease

THE last 50 years have seen a dramatic change in the pattern of disease affecting man. In the first part of this century infection and malnutrition were the most important causes of morbidity and mortality, but these conditions have largely been eliminated in wealthy industrialised nations and are being controlled in developing, poorer, countries. Recently attention has been turning increasingly to problems presented by malignant disease, degenerative disorders, biochemical disturbances, immunology, and mental illness. It has also become apparent that many disorders are largely, or even entirely genetic in origin. There are many reasons for this change in emphasis. For example, in one recent extensive survey more than 40 per cent of childhood deaths were due to genetic disorders. There is increasing awareness that chromosomal damage can be caused by ionising radiation used in therapy or from environmental pollution; the consequences of the latter on the future of the human race is an aspect which is widely discussed at the present time. That reactions to certain drugs can be due to inherited sensitivity is another instance. Parents are more aware today than ever before of the dangers of the transmission of genetic disorders to their children, and are often well informed about these matters from newspapers, radio and television.

It is therefore essential that students and doctors should keep abreast of developments in the field of genetics so that they are able to appreciate the implications of inherited predisposition to certain disabilities; in addition they can use this knowledge to advantage in the anticipation and early recognition of disease and can discuss intelligently with their patients problems arising from genetic factors.

Cell Division and Reproduction

One of the fundamental characteristics of a living organism is the ability to reproduce itself. This can be achieved in the simpler plants and animals by binary fission. However, unless there is a mechanism for conjugation with other individuals, with exchange of genetic material, the stock soon becomes degenerate. In higher organisms the two processes of fission and conjugation have become very specialised. Both are illustrated in Figure 1. The first is represented by *mitosis*, a mechanism for maintaining the constancy of genetic material in the cells of any one organism.

The second process, *meiosis*, is concerned in the formation of germ cells for reproduction of a new organism. It ensures sufficient interchange of genetic material to preserve or even improve the vitality of the stock. Normal somatic cells in a particular species have a constant number of paired chromosomes in the nucleus; the total number of chromosomes is 46 in man. In meiosis there are essentially two divisions, the final result of which is the production, from a single parent cell with 46 chromosomes, of four cells each with 23 chromosomes. In the male each of these four cells forms a spermatozoon; in the female unequal division of the cytoplasm results in the formation of one large cell which matures to form an ovum and three small cells (the polar bodies) which later degenerate.

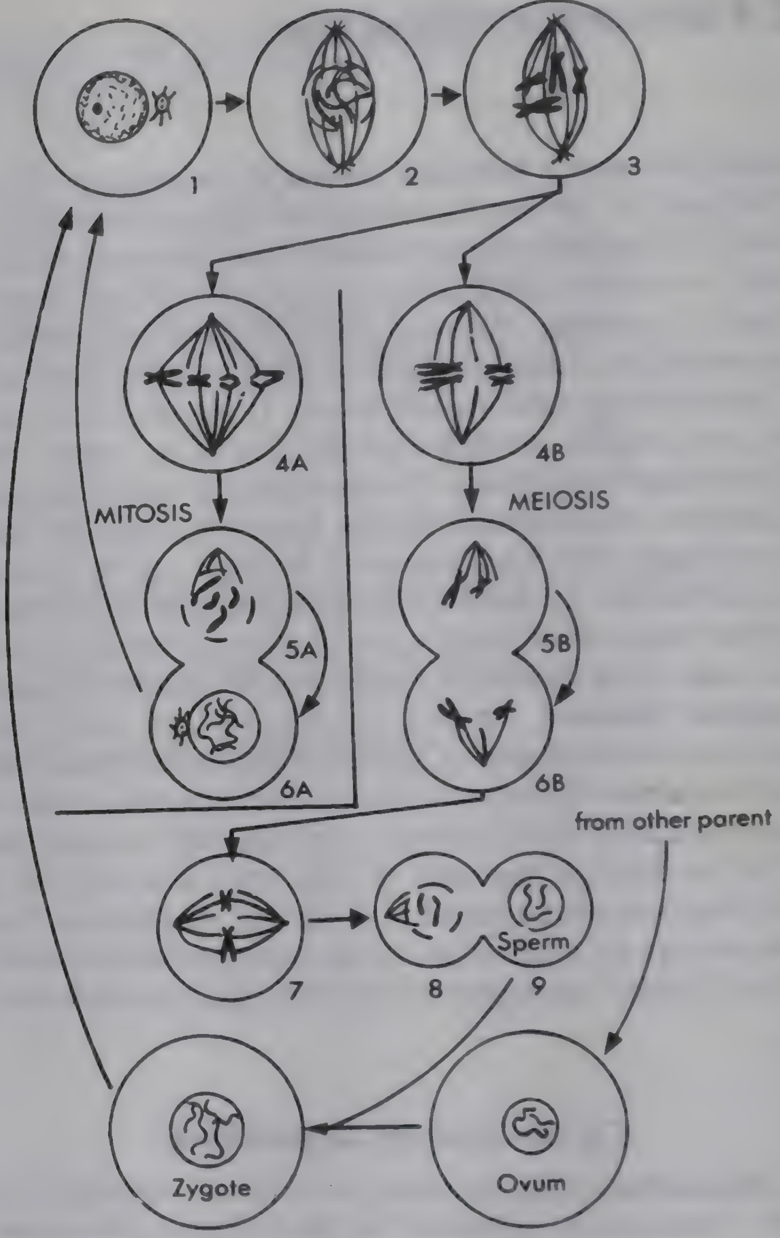


FIG. 1

CELL DIVISION AND REPRODUCTION

For illustrative purposes only four chromosomes are shown in the nucleus. On the left is the common division, mitosis. Stages 1, 2 and 3 show the appearance of chromosomes and chromatids (prophase). Stage 4A is metaphase when the chromosomes are arranged in the equatorial plane of the cell. Stages 5A and 6A, anaphase and telophase respectively show the separation of the chromosomes and cleavage of the cytoplasm to give rise to two daughter cells identical with the parent cell. On the right is meiosis. In the first division (reduction division), Stages 1, 2, 3 and 4B to 6B, two cells are produced each containing one member of every pair of chromosomes in the parent cell. Then follows a second division, Stages 7, 8 and 9 similar to mitosis which gives rise to spermatozoa or ova.

When a spermatozoon fertilises an ovum each contributes 23 chromosomes to the reconstitution of a nucleus in the zygote (fertilised ovum) with 46 chromosomes, and a new cell capable of production of a new individual is created. Normal human chromosomes have been classified into seven groups (known as groups A to G) depending on an estimation of their total length and on the position of the centromere. The centromere is the point of attachment of the chromatids to each other, and to the spindle (Fig. 1, 4A) and appears as the point of constriction in metaphase chromosomes. Identification of individual chromosomes can be achieved using these characteristics, the presence or

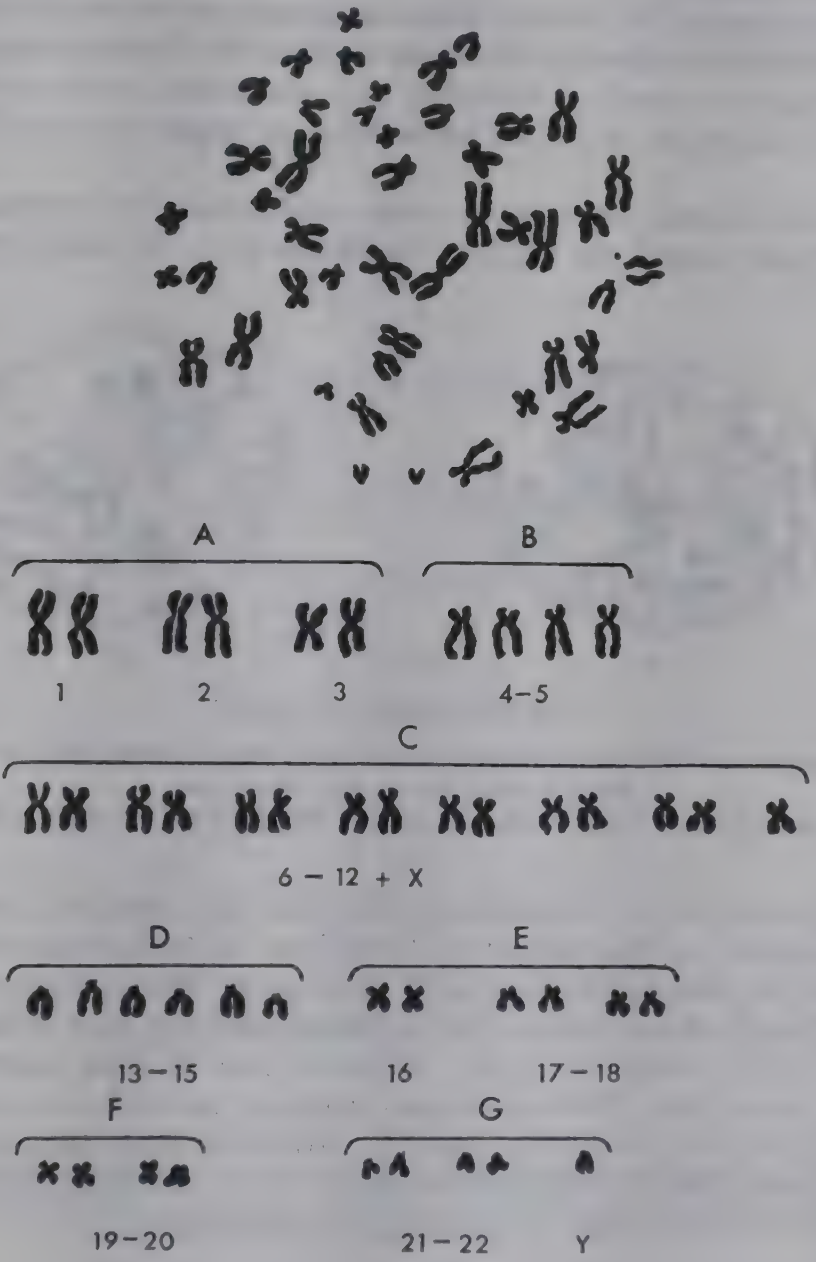


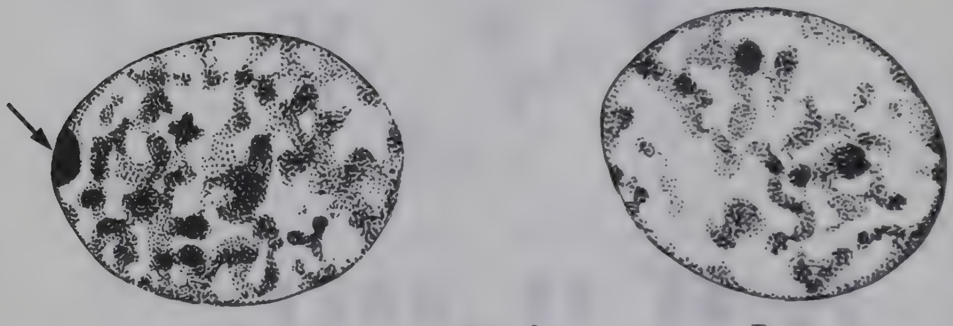
Fig. 2

Normal Human Male Karyotype

absence of small satellites which are attached to some chromosomes and various other techniques. Still more precise identification of individual chromosomes is possible by studying the banding patterns produced by certain fluorescent dyes and Giemsa stains.

Of the 23 pairs of normal human chromosomes, 22 are homologous; they are known as *autosomes* and when arranged in order of diminishing length they may be numbered from 1 to 22 (Fig. 2). The members of the remaining pair of chromosomes are known as the *sex chromosomes*. In the female, sex is determined by inheriting from each parent two sex chromosomes that are alike, the X chromosomes. In the male the members of the pair are dissimilar; his sex is determined by an X chromosome from his mother and a smaller and different one called the Y chromosome from his father. Hence in the normal somatic cell nucleus of the female there are 22 pairs of autosomes plus XX sex chromosomes, while in the male there are 22 plus XY. The chromosome pattern of an individual in respect of numbers, size and shape of the chromosome is known as the *karyotype*; a typical normal human male karyotype is illustrated in Figure 2.

In cells from normal females a minute condensation of nuclear chromatin can be seen lying against the nuclear membrane (Fig. 3). Such female cells are sometimes spoken of as *chromatin-positive* (or Barr-positive); male cells are *chromatin-negative* (or Barr-negative). Cells from the buccal mucosa are particularly suitable for study ('buccal smear'). The sex chromatin body is now known to be one of the X chromosomes that is inactive and the blob of deeply staining material is tightly coiled DNA. It is believed that in early embryonic life in the female one of the X chromosomes becomes partially or completely non-functioning. There is always one less sex chromatin body than the number of X chromosomes; a cell with XXX constitution (p. 11) will have two sex chromatin bodies, while there are none in a cell of XO constitution.



A FIG. 3 B

THE SEX CHROMATIN BODY

A Chromatin-positive cell from a female patient showing the condensation of nuclear chromatin lying against the nuclear membrane.

B Chromatin-negative cell from a male patient; no sex chromatin body is present.

The Nature of Genetic Material

Genetic material is concentrated in bands in the chromosome (chromomere segments), and developmental effects can be shown to result from deletions or additions of very small fragments of the chromosomes. The term '*gene*' is used to describe the factor at a particular point, or locus, on the chromosome which represents an individual hereditary characteristic, and contrasting or alternative forms of the gene are spoken of as *alleles* (allelomorphs). For example the genes for the A, B and O blood groups are multiple alleles at one locus. When alleles at the same locus on homologous chromosomes are identical, the individual is said to be *homozygous* for that gene or characteristic; when different he is said to be *heterozygous.*

The first advance in the understanding of the nature of inheritance came from the finding of deoxyribonucleic acid (DNA) in the chromomeres and then the demonstration that this was the substance in extracts from pathogenic capsule-forming pneumococci which could confer pathogenicity and capsule formation on pneumococci without these features. DNA has now been established as the ultimate carrier of genetic information; except for certain viruses which contain only ribonucleic acid (RNA), it is present in the cells of all reproducing organisms.

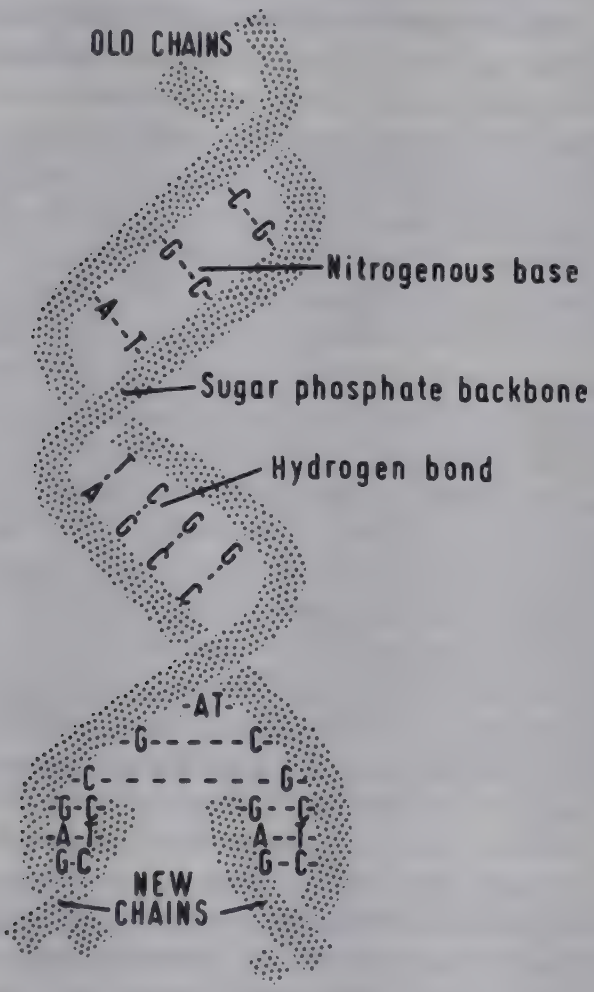


FIG. 4

The DNA molecule, composed of two chains of nucleotides, the backbone of each chain being formed by sugar-prosphate molecules. During replication the two chains separate while complementary chains are being synthesised.

(From Emery: *Elements of Medical Genetics.* 1974, 3rd ed. Edinburgh and London: Churchill Livingstone.)

The capacity of genes for identical replication is due to the unique structure of the DNA molecule, a long double strand in helical formation made up of many thousands of mononucleotides. According to the Watson-Crick DNA model (Fig. 4), the backbone of each strand is formed by sugar-phosphate molecules and the strands are held together by hydrogen bonds between the four nitrogenous bases, adenine, cytosine, thymine and guanine, which make up each strand. Experimental work on micro-organisms has shown that it is the sequence of these bases that determines the genetic information transmitted; a change in the sequence causes a change in genetic information or *mutation*.

It is now generally agreed that the primary action of genes is to specify the amino acid sequence of a particular protein or of one polypeptide component of a protein. These proteins may be either definitive proteins (e.g. collagen, haemoglobin) or enzymes and it is a useful concept that one particular gene or group of genes is concerned solely with the production of one polypeptide. The genetic 'code', the specific information which controls protein synthesis and determines the structure of individual proteins, is contained in the chromosomal DNA; protein synthesis however occurs mainly in the ribosomes in the cell cytoplasm. The precise mechanism of transference of genetic instruction from the chromosomes to the ribosomes is still uncertain but it is likely that this is a function of RNA (a smaller molecule than DNA in which ribose replaces deoxyribose and uracil replaces thymine). It now seems clear that some molecules of RNA (transfer-RNA) bring amino acids from the cytoplasm to the ribosomes while other molecules of RNA (messenger-RNA) are concerned with bringing instruction, the genetic code, from the chromosomes regarding the specific make-up of individual proteins. Messenger-RNA then acts as a form of template on which the amino acids can be laid down in the correct sequence.

If mutation occurs in the chromosomal DNA, and there are many sequences of bases concerned with the synthesis of a complex protein that are vulnerable, then the mutant gene may give rise to a different protein (or enzyme) or perhaps to no protein at all. An example of the production of a different protein is sickle cell disease (p. 737) in which the main abnormality is production of haemoglobin with properties differing from normal adult haemoglobin due to the replacement of glutamic acid by valine in the β polypeptide chain of the globin moiety; sickle haemoglobin is much less soluble than normal haemoglobin and tends to precipitate in the erythrocytes producing abnormally shaped red cells (sickle cells) which are more easily haemolysed. A typical example of loss of an enzyme is phenylketonuria which results from deficiency of a specific liver enzyme (L-phenylalanine hydroxylase) necessary for the conversion of phenylalanine to tyrosine; in consequence phenylalanine and related compounds accumulate in the body in excessive amounts, causing mental deficiency if not detected early in infancy.

The Pattern of Familial Disorders

One of Mendel's pioneer concepts was that the genetic information from both parents is transmitted to the next generation unchanged and the appearance of new characteristics due to the assortment and segregation of paternal and maternal genes. Such simple Mendelian laws are the basis of inheritance in man but it is with mutant genes having harmful effects that this pattern of behaviour in families can be most easily discerned.

Many factors influence a pedigree pattern. There are two main ones. The first relates to the 'expression' (i.e. the production of disease which is evident clinically) of the mutant gene and the second to the type of chromosome on which it is located. If the effects of the gene are evident in a single dose, i.e. the affected individual is heterozygous for the particular gene then the trait is said to be '*dominant*'. If on the other hand, the character is expressed only when the mutant gene has been inherited in double dose, i.e. from both parents and the individual is homozygous for the gene, then the trait is said to be '*recessive*'. Secondly the mutant gene may be located on an autosomal chromosome or on a sex chromosome; the inheritance of the abnormal trait is then described as autosomal or sex-linked respectively.

Autosomal Dominant Traits. The mutant gene is contributed by the affected parent on one of the autosomes and in the classical examples such as neurofibromatosis (p. 886), Huntington's chorea (p. 878) and hereditary haemorrhagic telangiectasia (p. 760) there is a one in two chance of the children of any affected individual also being affected, be they males or females. In general, dominant traits tend to be less severe than recessive.

The inheritance of dominant traits is not always straightforward in terms of Mendelian laws. In many conditions there tends to be a wide variation in severity and occasionally a heterozygote may appear perfectly healthy. In this case the gene is said to be *non-penetrant*. From detailed family studies it is possible to speak of 90 per cent, 50 per cent or 10 per cent penetrance depending on the proportion of individuals who are known to have inherited a particular mutant gene and are affected. A dominant trait, frequently showing *variable penetrance*, is congenital spherocytosis (p. 736); whole generations may be skipped—at least the trait is not detectable in them by present methods. Variation in expression of a dominant gene is difficult to explain; when it occurs it may be due to modification of the action of the abnormal gene by the recessive allele on the other chromosome.

Autosomal Recessive Traits. These also occur equally in the two sexes. Both parents, though outwardly normal, are heterozygous for the recessive trait and each affected child will be homozygous, having a double dose of the mutant gene. In general there is a one in four chance of the progeny from parents who are heterozygous carriers of an abnormal recessive gene being homozygous for the gene and showing clinical stigmata; one-quarter will be homozygous for the normal allele and will be normal in respect of the particular characteristic, and one-half will be heterozygous like the parents. Because related individuals will tend to be heterozygous for a particular mutant gene more frequently than the general population, recessive disorders, particularly the rarer ones, tend to arise more often in children of consanguineous matings than in random marriages.

Often the terms 'dominance' and 'recessiveness' are relative. Biochemical disturbances can occasionally be shown in the heterozygous individual, although no clinical disease is present. Examples are phenylketonuria (p. 908) and hepatolenticular degeneration (p. 876); in the former, special studies of the carrier individual will show impaired ability to convert phenylalanine to tyrosine, while in the latter the synthesis of plasma copper oxidase is suppressed, suggesting in both instances partial (but subclinical) expression of the defect which causes disease in the homozygous state.

Intermediate Inheritance and Codominance. Not all genetically determined diseases are easily classified since they may present clinically in both the heterozygous and homozygous state, the effect differing in severity and quality. Examples are thalassaemia (p. 737) and sickle cell disease (p. 737). In both, the heterozygous individual may show definite clinical illness. In thalassaemia minor there tends to be chronic mild anaemia; in the sickle cell trait, although anaemia is uncommon there is an increased incidence of thrombosis. This phenomenon is described as '*intermediate inheritance*'.

Another pattern in which allelomorphic genes in a heterozygous individual have equal importance is described as '*codominance*'. The best example is seen in the inheritance of ABO blood groups; the heterozygote who acquires the A antigen from one parent and the B antigen from the other, produces red cells of group AB.

Sex-linked Inheritance. Some traits appear to be transmitted by mutant genes on the X chromosome; disease due to location of a mutant gene on the Y chromosome has not been described in man.

In the female who has two X chromosomes, sex-linked characteristics may be dominant or recessive. Since the male has only one X chromosome he is said to be 'hemizygous' in respect of characteristics on this chromosome; there is no allele on the Y chromosome corresponding to an abnormal gene on the X; hence sex-linked traits whether dominant or recessive in the female are always fully expressed in the male. Another feature of sex-linked inheritance is that a father cannot transmit a mutant gene (dominant or recessive) from his X chromosome to his sons because he gives his X chromosome exclusively to his daughters.

The best example of sex-linked recessive inheritance is haemophilia (p. 762). A haemophilic male may have inherited the mutant gene on the X chromosome contributed by his mother or he may be the result of a new mutation. He will transmit the characteristic to all his daughters (who will be heterozygous carriers) but to none of his sons. If a woman is a proven carrier of a sex-linked recessive disorder then on average there is a 1 in 2 chance that any of her sons will be affected and a 1 in 2 chance that any of her daughters will be carriers. Sex-linked recessive traits are not exclusively male diseases but are nearly always so. A female haemophilic would require to inherit the gene from an affected father and from a heterozygous carrier mother. Such an event is, of course, very rare in haemophilia. A much more common example of a sex-linked recessive trait in females is the one for colour blindness.

Sex-linked dominant inheritance occurs but is very rare. Both males and females are affected and both may transmit the disorder to their offspring. Superficially, sex-linked and autosomal dominant inheritance may appear to be similar; the critical difference is that an affected father in the former type transmits the disease to all his daughters but to none of his sons.

Multifactorial Inheritance. There are many fairly common conditions in which there is a definite familial tendency, the proportion of affected relatives being greater than in the general population. However, in these conditions the proportion is less than would be expected for any simple mode of inheritance and is usually of the order of 5 per cent. It seems likely that such conditions are caused by many genes and by the effects of environment, so-called multifactorial inheritance. In multifactorial inheritance it is assumed that there is an underlying graded attribute which is related to the causation of the disease. This is referred to as the individual's *liability*, which includes not only his genetic predisposition but also the environmental circumstances which render him more or less likely to develop the disease. The curve of liability has a normal distribution in both the general population and in relatives of persons with the disease, but the curve in the latter case is shifted to the right so that the proportion beyond an arbitrary threshold is greater in relatives than in the general population. Statistical models of this type are used to analyse measurable characters, such as stature and intelligence, and also to explain the familial incidence of such conditions as diabetes mellitus, schizophrenia, essential hypertension, peptic ulcer, ischaemic heart disease, rheumatoid arthritis, and ankylosing spondylitis as well as certain congenital malformations such as hare-lip with or without cleft palate, anencephaly and spina bifida, club foot and congenital pyloric stenosis. The contribution of genetic factors, as opposed to environmental factors, in the aetiology of a particular disorder can be expressed as a percentage which is referred to as the *heritability* (Fig. 5). In the above conditions this is usually of the order of 50 to 70 per cent.

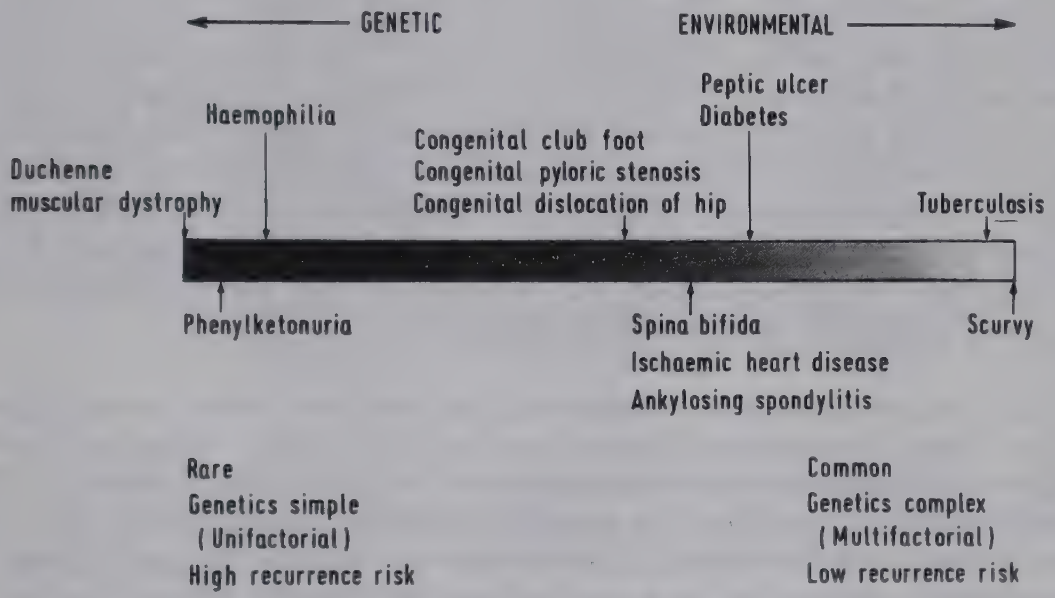


FIG. 5

SPECTRUM OF HUMAN DISEASES

These range from diseases which are entirely genetic in origin to those which are largely environmental in causation.

In multifactorial inheritance the empiric risk, i.e. the chance of occurrence in other members of the family, cannot be predicted from Mendelian principles and none has been due to monosomy. This is probably because many are lethal *in utero* or even before implantation of the ovum.

Several autosomal trisomic states are now recognised, the best known being Down's syndrome (mongolism). The others are rare and characterised by severe physical and mental retardation. In addition to these numerical abnormalities there may be structural changes (translocation or deletion) in the autosomes in chronic myeloid leukaemia or as a result of ionising radiation or in relation to abortion.

DOWN'S SYNDROME. This is due to trisomy of chromosome 21. In this condition the main abnormalities are mental retardation and stunting of growth in association with a number of distinctive features which include absence or poor development of the bridge of the nose, an oriental slant to the eyes, short curved little fingers, hyperextensible joints, broad palms with a single transverse palmar crease and spots of depigmentation in the iris.

Generally speaking the likelihood of occurrence of Down's syndrome is related to maternal age, presumably because of the increased risk of non-disjunction occurring in the ageing ovary. However, if a young mother (under 25 years) produces a child with Down's syndrome there may be a high risk of her producing another. This is because such children born of young mothers may be due to chromosome translocation. When this occurs the mother (or rarely the father) may have only 45 chromosomes, one of which is abnormal, comprising chromosome 14, 15 or 22 and genetic material translocated from chromosome 21. This abnormal translocation chromosome is transmitted to the child along with a normal chromosome 21 from the other parent. Such 'translocation mongols' who have only 46 chromosomes are effectively trisomic for chromosome 21, like the 'age dependent mongols' due to non-disjunction who have 47.

CHRONIC MYELOID LEUKAEMIA. In this condition (p. 750) chromosome 22 has almost half of its substance translocated to another chromosome. The abnormal chromosome 22, which is found only in the cells of bone-marrow origin, i.e. the granulocytes, erythroid precursors and megakaryocytes, has come to be known as the '*Philadelphia chromosome*'. It has diagnostic usefulness in doubtful cases of myeloid leukaemia. So far, though chromosome abnormalities are seen frequently in the other types of leukaemia and other malignant diseases, no consistent pattern has emerged.

IONISING RADIATION. Since ionising radiation is known to cause chromosome damage it is relevant to mention here the increased incidence of leukaemia and neoplasms that have been described in a number of groups exposed to excessive amounts, namely, the early X-ray workers, the survivors of the atomic bomb explosions in Hiroshima and Nagasaki and those receiving irradiation therapy for ankylosing spondylitis. Besides these *somatic* effects, exposure to radiation may also produce *genetic* effects (i.e. mutations) but the latter are usually not immediately evident in the present generation.

ABORTION. Not only do some families with chromosome abnormalities show an increased tendency to abortion, but also about 25 per cent of spontaneous abortions appear to be associated with visible chromosome abnormalities in the fetus. These findings indicate that many spontaneous abortions are not affecting normal fetuses; instead they are having considerable eugenic importance by reducing the total number of children born with chromosomal aberrations.

Genetic Advice

Doctors are being asked increasingly by their patients about genetic risks. Questions are raised by parents or young people contemplating marriage, who themselves have some disorder like epilepsy or some malformation like a hare-lip, about the danger of transmitting this to a child. Most enquiries come from parents who, having already produced an abnormal child, e.g. a mongol, wish to know the chances of subsequent children being affected. Cousins will often wish to discuss the hazards of consanguinity (in Britain there are about 6 cousin marriages per 1,000 unions). Adoption societies have special problems when handling children of mentally defective mothers. The doctor's responsibility for giving sensible advice on these matters is considerable because the whole subject is pervaded by emotion and superstition and much of the importance of genetic counselling lies in allaying the fears of the ill-informed.

Although it is not possible for the family doctor to be familiar with the many hundreds of conditions that are known to be due to mutant genes, he should have some knowledge of those disorders in which special genetic risks are involved. He also requires to know the principles underlying genetic counselling and where expert advice for his patients can be obtained. It is to meet this latter need that genetic counselling clinics are being established in main centres in this and other countries.

Some examples of conditions transmitted by autosomal dominant inheritance, when the risk to children of an affected parent is one in two, have already been given, e.g. Huntington's chorea. Multiple polyposis of the colon is another disease worthy of special mention because it illustrates the scope of the problem. This rare disorder, if inherited, carries a sufficiently high risk of malignant disease to justify prophylactic colectomy. Hence children of affected families require regular investigation of the colon until it is known which are at risk.

Recessive traits usually appear unexpectedly with no one else in the family being affected and therefore the diagnosis may not be made until it is too late for successful treatment. The risk that subsequent siblings will inherit the disease is one in four, and in the case of phenylketonuria, for example, if there is to be any value in treatment, prompt diagnosis soon after birth is essential. It is probably with recessive genes that genetic counselling before marriage will have its greatest value, particularly when further methods develop for recognising the carrier state. Already this is being applied to the problem of thalassaemia in parts of Italy where as many as 1 in 10 of the population carry the mutant gene (p. 8). The object of detection of the carrier state for thalassaemia by routine examination of school children is to warn and, if possible, prevent the intermarriage of carriers, as by this means the disease could be prevented. Elsewhere in Europe recessive genes do not cause the same public health problems but means of demonstrating with certainty the carrier for fibrocystic disease of the pancreas and haemophilia would be valuable. As stated above, the detection of the carriers of phenylketonuria and hepatolenticular degeneration is already possible. In addition, 70 per cent of the female carriers of the Duchenne type of muscular dystrophy (a sex-linked recessive trait) can be recognised by estimation of the enzyme creatine kinase in the serum (p. 906).

As has been discussed, the risk of a further child with Down's syndrome being born to a woman over 25 years is only slightly increased since this child has probably been produced by an accident of disjunction. However, the young mother may have produced a translocation mongol due to a fixed abnormality in her genetic make-up and the chance of her producing another mongol baby is about one in ten or greater. Such a problem can be resolved only by a knowledge of genetic prognosis based on chromosome examination. Hence the value of having genetic laboratories associated with genetic clinics.

In the case of more common disorders research is gradually establishing the chance of occurrence in other members of the family. For example the empiric risk of later siblings being affected is about 1 in 20 for anencephaly and spina bifida, less than 1 in 25 for congenital heart disease, and 1 in 50 for cleft palate. In conditions where affected persons survive, the risks of their having an affected child are of the same order as the risks to subsequent siblings when normal parents have an affected child. However, if an affected parent has already had an affected child the risk in subsequent children is significantly increased, e.g. 1 in 6 for cleft palate.

The risk of a normal woman with a normal husband producing a child with serious congenital malformation is about 1 in 40. This gives the geneticist some degree of perspective on which to base his assessment and his advice. It is generally agreed that a genetic risk exceeding 1 in 10 is a bad risk, while one of less than 1 in 20 is a good risk. Fortunately most genetic problems divide clearly into one or other of these categories.

A recent development has been the study of amniotic fluid cells obtained by amniocentesis in early pregnancy. By this technique it is possible to diagnose chromosome and certain inherited biochemical disorders in the fetus. In this way parents at risk of having a child with certain serious genetic disorders may be guaranteed an unaffected child by selective abortion of any fetuses which prove to be affected.

A. E. H. EMERY.
JOHN RICHMOND.

Further reading:

Emery, A. E. H. (1974). *Elements of Medical Genetics*, 3rd ed. Edinburgh and London: Churchill Livingstone.

Emery, A. E. H. (editor). (1973). *Antenatal Diagnosis of Genetic Disease*. Edinburgh and London: Churchill Livingstone.

Immunological Factors in Disease

THE science of immunology arose from the study of man's resistance to infection. The most striking feature of this resistance is the specific nature of its enhancement in individuals following infection. Thus, antigenic stimulation and antibody production began to be elucidated in the context of infectious disease and immunity to it. Terms such as 'immunology', 'immunisation' and 'specific immune response' are derived from these origins.

It soon appeared that such specific 'immune' responses might also confer unpleasant and sometimes dangerous hypersensitivity to subsequent exposure to the provoking antigen. Resistance to infection is not an essential feature of the immune response; for example, bacteria may induce antibodies which have no obvious protective value and immune responses are often evoked by injection of intrinsically harmless non-living organic substances, such as serum protein from another individual or species. After exposure to antigen the individual develops a changed reactivity. The ability to develop specific immunity to infection is only one consequence of a wider capacity in the individual to recognise and to respond specifically to the foreignness of a wide range of biological substances that are not normally present in his own tissues. Immunology is the study of what this 'changed reactivity' or allergy is in terms of cellular biochemistry, how it is brought about, and how it is regulated both quantitatively and qualitatively. In the present chapter an account of current concepts of the physiology of the immune system is given in order that the clinical application of immunology may be understood in relation to such diverse conditions as infection, asthma, drug reactions and certain endocrine, gastrointestinal, haematological and connective tissue disorders.

The antigenicity of a substance (i.e. its ability to induce an immune response) is determined by one or more specific molecular groups on its structure known as antigenic determinants. When immunocompetent lymphocytes recognise a foreign substance (antigen) they respond by undergoing transformation into lymphoblasts and then antibody-producing plasma cells or lymphocytes as indicated in Figure 6. It is considered that the population of antibody-producing cells arises by random mutation and that a single cell will then react to produce a family of cells (clone) with a specific function. Essential to this concept is that random mutation of lymphocytes allows the production of cells that are capable of responding to all antigens, although a single cell can react to only one antigen. Antibody-production is a special example of protein synthesis, i.e. the putting together of amino acids to form protein molecules, in this instance, immunoglobulins, and the replication of this process according to a pattern. Its special feature is that it involves a synthesis that can be varied on demand to produce different antibodies capable of reacting to any of the many different antigenic determinants.

If antigenic material (either part of self or a foreign substance) comes into contact with the cells of the antibody-forming system at the stage before the cells have reached maturity, e.g. in fetal life, the result is a failure of response rather than stimulation of antibody formation or other form of immune response against the antigen concerned. This is referred to as immunological tolerance to the antigen. Probably for this reason an individual does not normally show an immune response against components of his own tissues. In the abnormal situation where an immune reaction does occur to a component of the body's own tissues, the reaction is referred to as autoimmune.

The importance of transplantation in modern surgery gave a great impetus to the study of tolerance. The mechanisms underlying the rejection of tissues such as skin, kidney or heart from other individuals are immunological, the recipient reacting to foreign antigens in the donor tissue. Two antigen systems are known to influence graft compatibility in man: the ABO blood groups and the HL-A antigens on leucocytes and other cells. Other antigen systems are probably also involved. Matching for ABO compatibility presents no difficulties but, because of their complexity, matching for HL-A antigens (tissue typing) is not fully developed. Grafts are accepted only when these antigens are exactly the same in the recipient and donor if no methods are used to control the immune response. This occurs only in the case of identical twins or individuals from highly inbred strains of animals, such as mice, whose genetic constitution is identical. A skin graft from a genetically different individual of the same species (allograft) applied for the first time becomes vascularised and appears healthy for 13 to 14 days, depending on the degree of genetic difference between the donor and the recipient. The circulation then begins to fail, the graft becomes infiltrated with inflammatory mononuclear cells, and later necrotises and sloughs. If a second similar graft is now applied to the same recipient there is an accelerated and greatly increased inflammatory reaction with rapid necrosis. Sloughing of the graft occurs within three to four days, indicative of the development at the first exposure of an active immunity to the antigens of the donor tissue. Even when there is a lapse of time after the first acquaintance with the antigen, the cells of the immune system retain a memory of the antigen and are stimulated rapidly by further contact with the antigen. This augmented and accelerated secondary response not only involves cell mediated immunity but is also well recognised in the classical immunology of bacterial infection in relation to the levels of circulating antibody.

COMPONENTS OF THE IMMUNE SYSTEM

The main cells involved in immune reactions are lymphocytes, plasma cells and macrophages. Anatomically, the immune system can be subdived into the 'central' and 'peripheral' lymphoid tissues. The central lymphoid tissue consists of the thymus and the cloacal lymphoid organ in birds known as the bursa of Fabricius. In mammals the tonsils and the lymphoid tissue of the gut may well represent the analogue of the bursa of birds. The major peripheral lymphoid tissues are the spleen and lymph nodes.

The development of the immune mechanism depends on the evolution of the thymus and organised lymphoid tissues. The time at which a developing vertebrate can first react immunologically by rejecting skin grafts and by antibody production coincides with the period when lymphocytes can first be identified in the circulation. The thymus in mammals arises as a paired structure from the endoderm of the third branchial pouch but also acquires cells of other origins. The thymus gland increases in size until puberty and then slowly atrophies, but is still present even in old age.

The fully developed thymus is incompletely divided into lobules composed of a central medulla surrounded by a cortex. The cells in the thymus are of three main types: lymphocytes, ephithelial cells and mesenchymal cells. The lymphocytes, which look the same as those in the circulation or in lymph nodes, are heavily concentrated in the cortex. An epithelial lattice or reticulum invests all thymic lymphocytes; it is inconspicuous in the cortex but prominent in the medulla. Electron microscopic studies have suggested that some of the epithelial cells of the medulla may contain a stored secretion.

The rate of small lymphocyte production is very high in the thymus and is comparable to the rate of division in lymph nodes under conditions of maximal antigenic stimulation. However, the unique feature of the lymphopoiesis in the thymus is that it is not dependent on antigenic stimulation, nor is it affected by resection of other lymphoid organs, partial thymectomy or by the presence of one or numerous thymus implants. This suggests that the primary stimulus for the proliferation of thymic lymphoid cells must arise from within the thymus itself.

Immune reactions are mediated by humoral or cellular mechanisms or by both. The humoral factor consists of antibody (immunoglobulin) secreted by plasma cells. The cellular component is made up of lymphocytes sensitised to specific antigens and reactive with those antigens without the presence of free antibody. In addition, certain lymphoid cells, although not themselves specifically sensitised, can gain specificity in the presence of antibody or antigen-antibody complexes on the surface of the target cells or on their own surface. This is known as lymphoid cell-dependent antibody-mediated cytotoxicity (type VI reaction, Figs 6 and 13). The lymphoid cells involved are referred to as killer or K cells.

Immunological responses mediated by humoral antibody and by cells both depend initially upon the activity of small lymphocytes which initially stem from precursors in the bone marrow. The main effect of neonatal thymectomy is to prevent the development of cell-mediated immunological reactions such as allograft rejection, although the humoral antibody response to certain antigens is also impaired. In birds antibody production, but not cell-mediated reactions, is dependent on the bursa of Fabricius. These and other findings suggest that stem-cells originating in the bone marrow differentiate to form two main lymphocyte populations. One is dependent on the presence of the thymus (T lymphocytes) and is responsible for cell-mediated hypersensitivity. The other is independent of the thymus but dependent on the bursa of Fabricius or its equivalent in man (B lymphocytes, Fig. 6) and is responsible for humoral antibody synthesis. They also differ in their distribution and probably in their life span. T lymphocytes constitute a greater part of the pool of small lymphocytes that circulate in the blood, interstitial spaces and lymph (Fig. 7) and most of them have a relatively long life (months or years in man) while the B lymphocytes are more restricted to lymphoid tissue and most of them appear to be short-lived (several weeks). There is evidence for the existence of sub-classes, presumably with differing functions, within these main classes; e.g. short-lived T lymphocytes and long-lived B lymphocytes. Thus immunological memory is achieved by the existence of long-lived T and B cells.

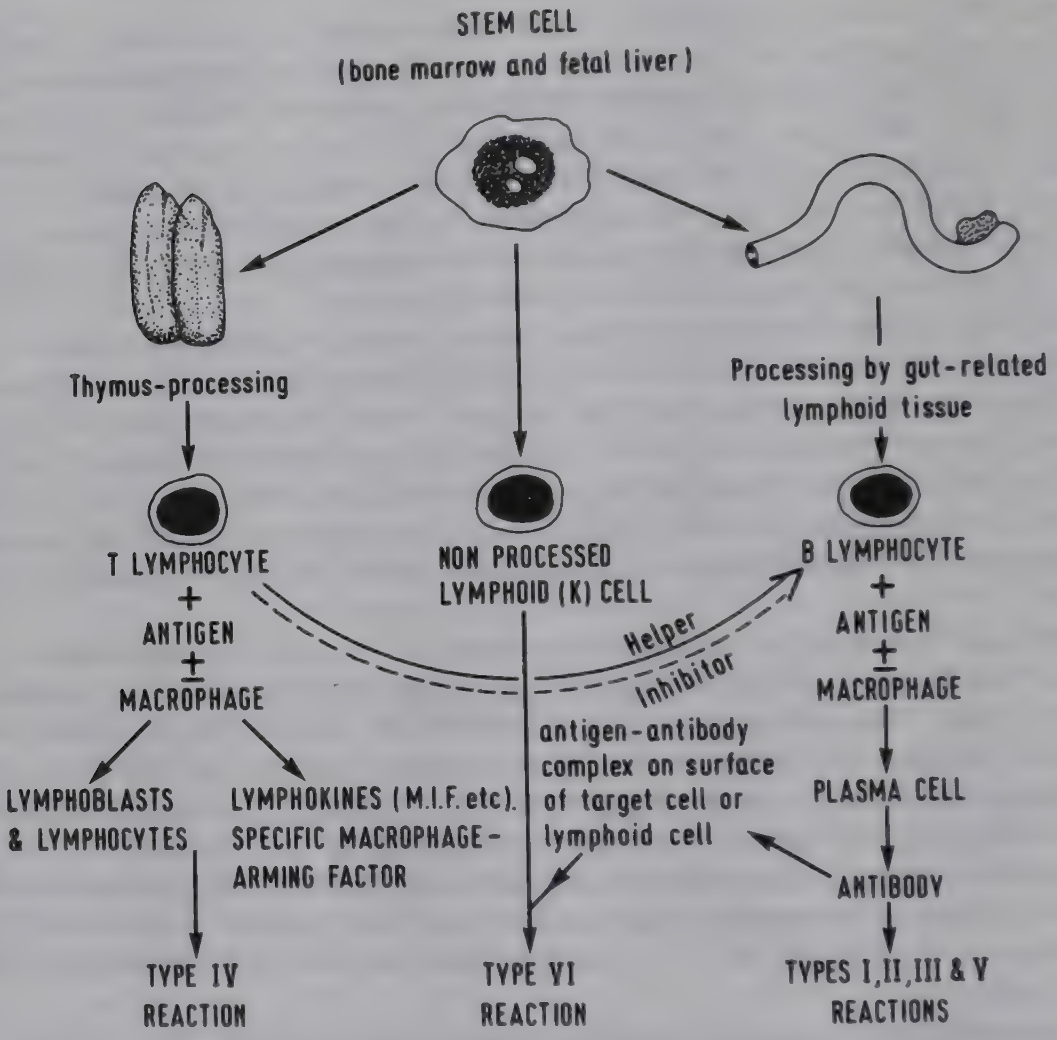

STEM CELL
(bone marrow and fetal liver)
Thymus-processing
Processing by gut-related lymphoid tissue
T LYMPHOCYTE
+
ANTIGEN
±
MACROPHAGE
NON PROCESSED LYMPHOID (K) CELL
B LYMPHOCYTE
+
ANTIGEN
±
MACROPHAGE
Helper
Inhibitor
antigen-antibody complex on surface of target cell or lymphoid cell
LYMPHOBLASTS & LYMPHOCYTES
LYMPHOKINES (M.I.F. etc). SPECIFIC MACROPHAGE-ARMING FACTOR
PLASMA CELL
ANTIBODY
TYPE IV REACTION
TYPE VI REACTION
TYPES I, II, III & V REACTIONS

FIG. 6

Role of T lymphocytes, B lymphocytes and non-processed lymphoid cells in immunological responses. Many of these events involve active cell proliferation, but for simplicity this has not been shown.

(From Irvine, *Proceedings of the Royal Society of Medicine*, 1974.)

The thymus plays an essential role in inducing the differentiation of immunologically competent thymus-dependent lymphocytes (T cells) from non-competent precursors. This function is dependent upon the integrity of the epithelial cells in the thymic medulla which secrete a factor or hormone that effects this change (Fig. 7).

Unlike thymectomy in the newborn, thymectomy in adult life leads to no immediate significant impairment of immuno-capacity although there may be some reduction in the population of lymphocytes in the peripheral blood, thoracic duct lymph, lymph nodes and spleen. If, however, the lymphoid system in the adult mouse is damaged or destroyed by ionising radiation, then the thymus is important for the anatomical and functional regeneration of this system. Furthermore, when animals thymectomised in adult life are challenged with a new antigen six or more months later, there is clear evidence of immunological deficiency. Presumably the adult thymus influences the development of an adequate population of long-lived immunologically competent cells. Only when this pool has become depleted, as a result of the limited life span of its cells, do defects in immune capacity become apparent. The thymus is thus not only essential for the development of the immunological system during the neonatal period but is also important for the maintenance of immunological function in the adult.

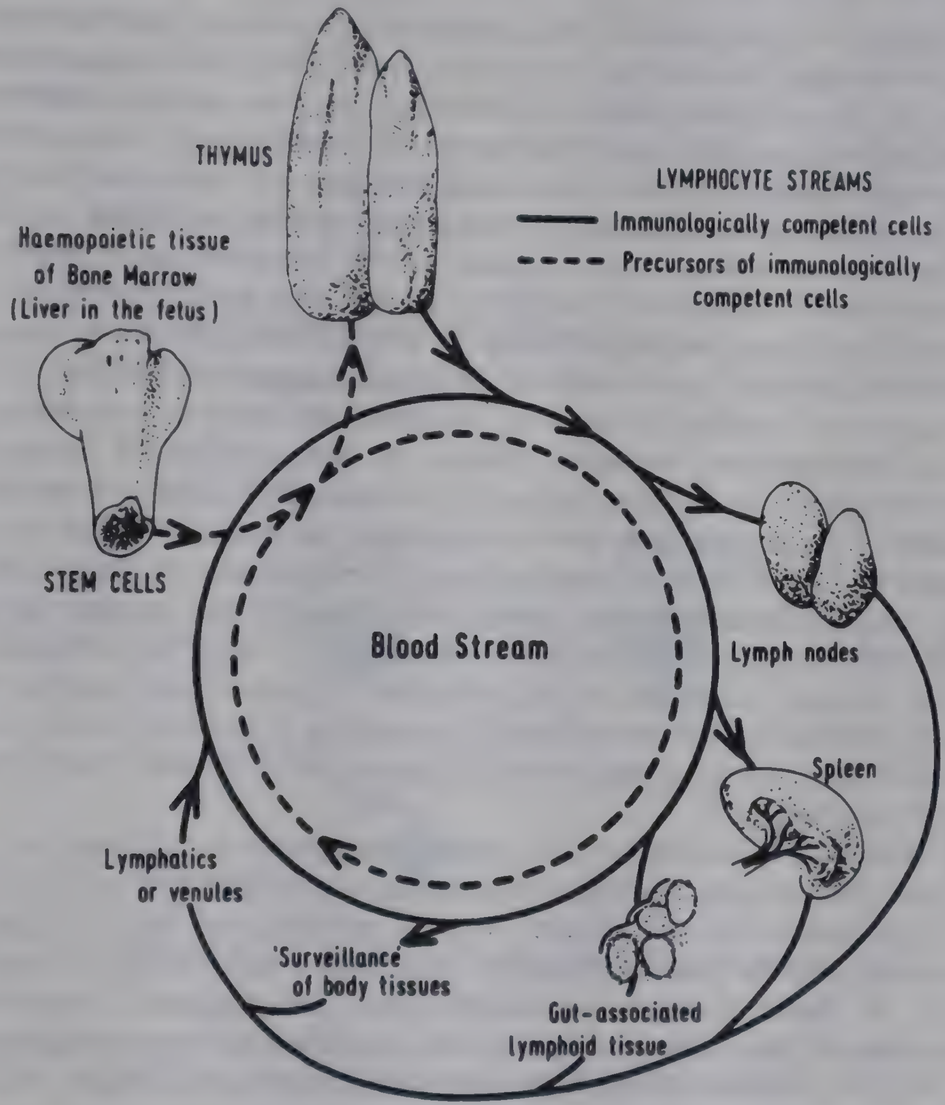

THYMUS
LYMPHOCYTE STREAMS
Immunologically competent cells
Precursors of immunologically competent cells
Haemopoietic tissue of Bone Marrow (Liver in the fetus)
STEM CELLS
Blood Stream
Lymph nodes
Spleen
Lymphatics or venules
'Surveillance' of body tissues
Gut-associated lymphoid tissue

FIG. 7

THE THYMUS AND IMMUNOLOGICAL COMPETENCE

Diagram to show circulation of lymphocytes in the body. Lymphopoietic stem-cells arise in the bone-marrow and reach the thymus via the blood stream. Within the thymus stem-cells become immunologically competent lymphocytes (T cells), emigrate to the blood stream, and circulate between the tissues, lymphatics and blood stream.

(From Goldstein and Mackay, *The Human Thymus*, 1969. London: Heinemann.)

About 70 per cent of lymphocytes in the peripheral blood are T cells and about 20 per cent are B cells. The non-sensitised lymphoid cells that are neither

T nor B cells but can gain specificity by means of antibody or antigen-antibody complexes (K cells) are included in the remaining 10 per cent.

MECHANISM OF THE IMMUNE RESPONSE

The recognition of antigen by B lymphocytes is believed to be mediated by antibody synthesised in the cell and bound into the surface membrane, the specificity of the antibody being determined by the genetic characteristics (programming) of the individual lymphocyte. T lymphocytes, on the other hand, do not have detectable antibody on their surfaces but have antibody-like receptors, the exact nature of which is not clear. In both instances combination with the appropriate antigen then triggers off the immunological response.

The induction of mitosis in T lymphocytes and their transformation to larger 'blast' cells (Fig. 6) may be effected both by specific antigens and by non-specific mitogens which include agents such as phytohaemagglutinin (PHA). It is likely that stimulation of mitosis in some T lymphocytes involves processing of the antigen by macrophages, possibly leading to presentation of antigen determinants at the surface of the macrophage. For example, lymphocyte preparations largely freed of phagocytic cells are unresponsive to certain antigens but activity can be restored by addition of macrophages. Lymphocytes in tissue-culture can be seen to wander incessantly and presumably identify the antigens of the cells over which they move in terms of their degree of 'fit' with the antibody on the lymphocyte surface. Likewise, in the body the T lymphocytes migrate through the tissues (immunological surveillance) permitting their sensitisation or transformation to blast cells by contact with antigen in the periphery, with or without the help of macrophages.

The T lymphocyte sensitised to a specific antigen is a cytotoxic cell and on contact with the antigen undergoes blast transformation and proliferation. In addition, the interaction of antigen with T lymphocytes leads to the release of non-specific soluble factors (lymphokines, Figs 6 and 16) which bring about a number of tissue changes associated with cell-mediated hypersensitivity reactions. One of these factors inhibits the migration of macrophages in tissue culture. *In vivo* the effect of the migration inhibitory factor (MIF) would be to immobilise randomly wandering macrophages at the site of reaction with antigen, where they might exert a cytotoxic action or merely act as scavengers of cells already damaged by lymphocytes. Other non-specific factors released from the sensitised lymphocytes can increase vascular permeability, cause inhibition of growth or death of tissue cells, be chemotactic for mononuclear cells and stimulate mitosis in 'non-sensitised' lymphocytes. The release of lymphokines is an example of an amplification mechanism that augments the specific response initiated by relatively few cells. In addition to lymphokines, specific macrophage arming factor is released which renders macrophages cytostatic to cells bearing that particular antigen.

How B lymphocytes are stimulated to become the antibody-forming cells of the plasmocyte line is not yet fully understood. A possible sequence of events is shown diagrammatically in Figure 8. Certain antigens are apparently capable of reacting with the corresponding antibody on the surface of a B lymphocyte to induce it to transform and proliferate into active antibody-producing cells (plasma cells). Such antigens generally have many antigenic determinants of the same specificity so that they can simultaneously trigger a number of receptors on the surface of the same lymphocyte. Other antigens, or small doses of antigen, may have to be taken on to the surface of a macrophage, as mentioned above in relation to T lymphocytes, thus being more readily available for stimulating a B lymphocyte either directly or through the co-operation of a helper T lymphocyte. In this way a high local concentration of antigen is achieved during cell to cell contact with the B lymphocyte, thereby stimulating a greater number of receptor sites in a given cell than if the antigen were uniformly dispersed throughout the body fluids. Once stimulated, the cell undergoes division and produces the antibody that it is genetically programmed to do.

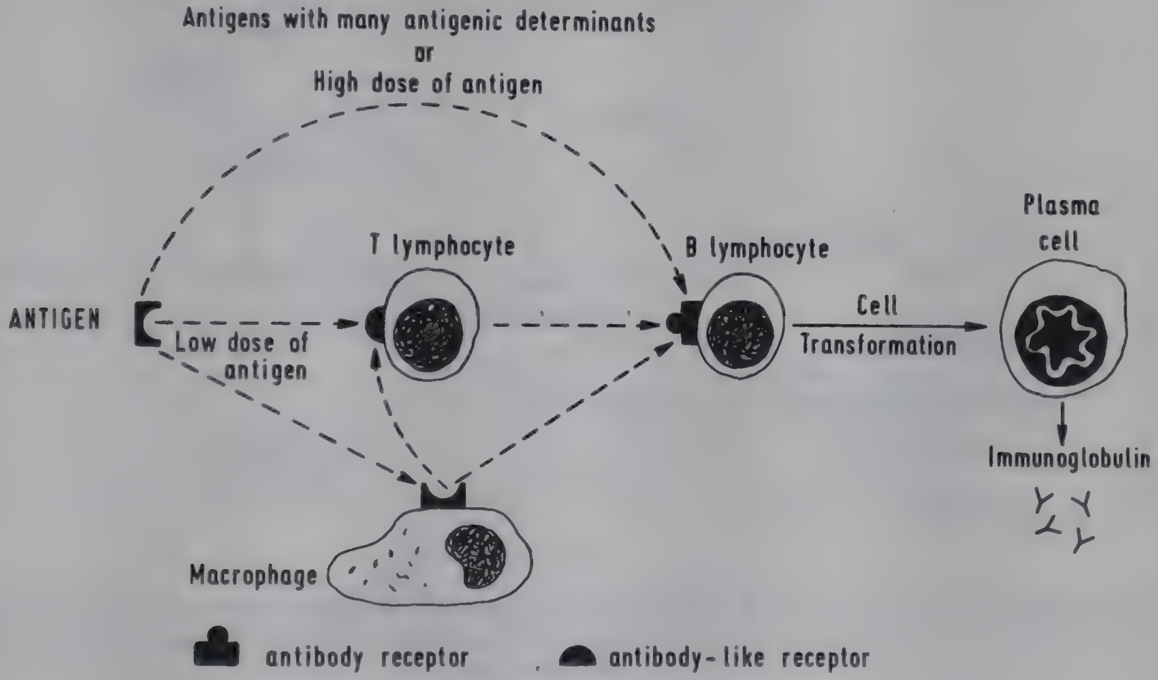


FIG. 8

Possible sequence of events in humoral antibody formation, illustrating co-operation between T lymphocytes, B lymphocytes and macrophages.

Another possible result of the interaction of certain types of antigens with the surface of a lymphocyte is that the cell is prevented from transforming for antibody formation and is functionally eliminated. The individual has immune tolerance to that particular antigen.

There is evidence for positive and negative control of immunological mechanisms as indicated in Figure 9. For example, the activity of helper T lymphocytes may be suppressed by the presence of excess antibody and the ability of B lymphocytes to respond to antigenic stimulation is subject to the influence of controlling T lymphocytes. The control mechanism is somewhat analogous to that which operates within the endocrine system.

Observations *in vitro* and *in vivo* have shown that continued division of lymphoblasts ultimately gives rise to progeny with the morphological characteristics of small lymphocytes, and this expanded population of lymphocytes with the same antibody specificity as the original parent cells may provide a basis for the immunological memory referred to above and which is a feature of both cellular and humoral responses. The lymphocyte population is therefore a heterogeneous group of morphologically similar cells.

The controlling mechanism illustrated in Figure 9 may be overcome by the incorporation of tissue antigen in an oil emulsion with an extract of tubercle bacillus (Freund's adjuvant) and its injection into the foot pads of an experimental animal. This causes a granuloma which enhances both cell mediated hypersensitivity and antibody production due to the antigen in the epithelioid cells of the granuloma providing a more effective stimulus for recruitment of T lymphocytes and/or to processing of the antigen by macrophages. In this way a normal animal can be induced to mount an immune response to its own tissues.

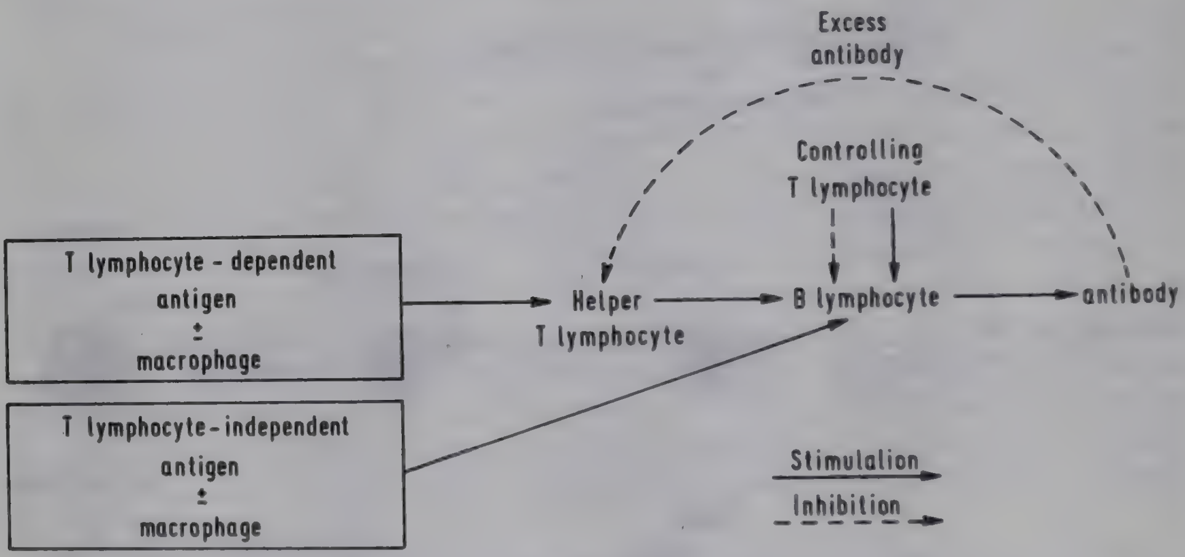


FIG. 9

The concept of the dual role of T lymphocytes in relation to B lymphocytes: (1) Helper function increases antibody formation; (2) Controlling function limits antibody formation (particularly autoantibodies).

(Based on Allison *et al.*, 1971. *Lancet* **2**, 135.)

Immunoglobulins

From the early days of immunology, antibodies have been described in terms of their various reactions with antigens as precipitins, lysins, antitoxins, agglutinins, etc. and it was believed that these effects were due to the same kind of antibody acting in different circumstances. It is now clear on two scores that not all antibodies reacting with the same antigen are of the same kind. Firstly, different antibodies may react with antigenic determinants of varying specificity on the same substance (e.g. a protein molecule). Secondly, the immunoglobulin classes (IgG, IgM, IgA, IgD and IgE) differ in their biological properties.

Structure of Immunoglobulins

Immunoglobulins are made up of distinct sub-units held together in the whole molecule by disulphide (S-S) bonds (Fig. 10). The bonds can be broken by reducing agents, so that the molecule falls apart into pairs of polypeptide chains called light and heavy chains as determined by their molecular weights. Two types of light chain exist, K and L, of which individual immunoglobulins have only one type. The enzyme papain splits the immunoglobulin molecule into two antigen binding (Fab) fractions and one crystallisable fraction (Fc). The Fc fragment of the heavy chain is responsible for the antigenic differences between the classes of immunoglobulin which enables their ready quantitation by antisera. It is the Fc fragment of the heavy chain which carries the predominant part of the molecule responsible for complement activation or fixation. This depends upon changes in the configuration of immunological molecules when they are brought into close apposition during reaction with antigen. The Fc fragment also contains sites for macrophage fixation and for fixation to the killer (K) lymphoid cells of Type VI reactions (Fig. 13).

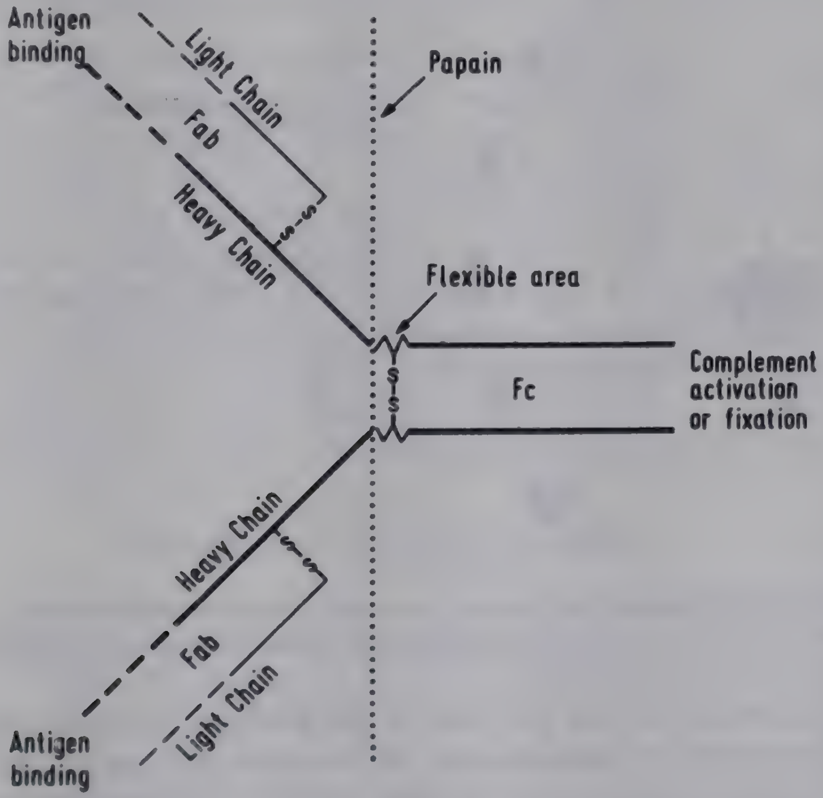


FIG. 10

Immunoglobulin structure. Note (1) Disulphide bond cleavage produces two light chains and two heavy chains. (2) The dotted line shows the site of papain cleavage producing two Fab portions and one Fc portion. (3) The amino acids that vary in sequence for different antibodies are shown as interrupted ends of the light and heavy chains and may represent the combining sites that determine the specificity of individual antibody molecules for their particular antigen.

CLASSIFICATION AND FUNCTIONS OF IMMUNOGLOBULINS

IgG. In healthy adults, the total IgG (about 80 g) accounts for 73 per cent of the immunoglobulins in normal serum and is distributed equally between the blood and interstitial tissues, about a quarter passing across the capillary walls each day and the same amount returning via the thoracic duct. In man, IgG is the only immunoglobulin that is transported across the placenta to reach the fetal circulation and provide the baby with passive immunisation during its early life. IgG antibody is particularly suited to neutralising soluble toxin such as that of *C. diphtheriae*.

IgM. The macro-molecular IgM is predominantly intravascular. It constitutes only 7 per cent of the serum immunoglobulins and is made up of five immunoglobulin units linked with disulphide bonds to provide ten identical combining-sites instead of the two of IgG. IgM is especially effective in activating complement to produce immune lysis of foreign cells by digesting holes in the cell membranes at the sites where antibody has reacted. Fifty micrograms/100 ml of IgM antibody could destroy half the red cells in the circulation. IgM antibodies are much more efficient than IgG antibodies in linking particulate antigens together for agglutination and phagocytosis and would seem to be specially adapted for dealing with cell debris or bacteria in the blood stream.

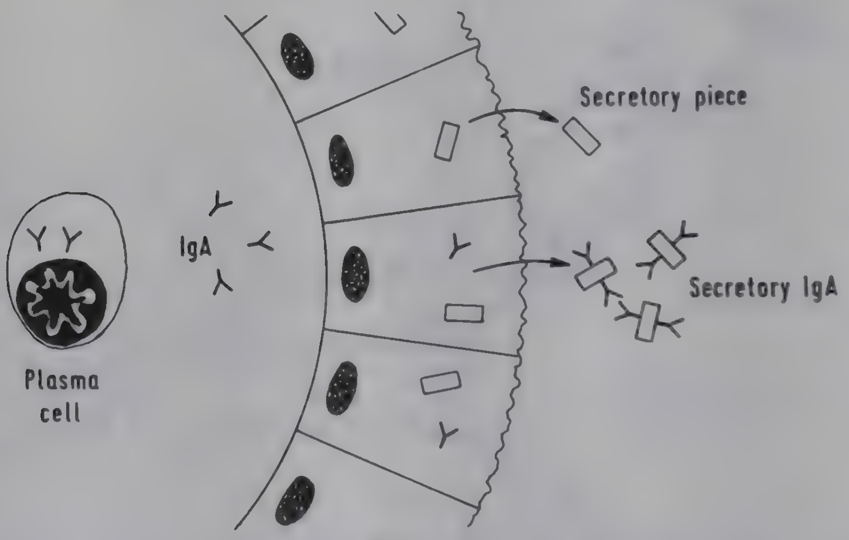


FIG. 11

The conversion of IgA produced by plasma cells (e.g. in the lamina propriae of the gut) to the more stable secretory IgA which bathes the mucous surfaces of the body.

IgA, which accounts for 19 per cent of the total serum immunoglobulins, is preferentially secreted into colostrum, saliva, intestinal juice and respiratory secretions. The major sites of IgA synthesis are the laminae propriae underlying the mucous membranes throughout the respiratory tract and the gut. The monomer produced locally by plasma cells is largely taken up by the epithelial cells, when two of them link together and a secretory piece (Fig. 11) is added which protects the molecule from digestive enzymes. Secretory IgA is available right through to the faeces and these antibodies are vital in the defence of the gut against enteroviruses, e.g. poliomyelitis. In general, IgA plays a major role as part of an antiseptic secretion over the mucous surfaces of the body.

IgD. These have some of the properties of the IgG globulins, although little is known of their exact role.

IgE. These have a very low serum level (250 pg/ml) and the distinctive property of possessing an affinity for cell surfaces. They have been implicated in various forms of immediate hypersensitivity such as hay fever and asthma (p. 376). The Fc portions of the IgE antibodies combine with sites on the surface of mast cells especially in the nasopharynx and bronchi and also in the gut, leaving the antigen-combining sites freely available. The combination of antigen (in this circumstance sometimes referred to as reagin) with IgE antibody on the surface of the mast cell triggers the release of vasoactive substances which mediate anaphylactic (immediate hypersensitivity) reactions (Figs 13 and 14). The physiological function of IgE antibodies is obscure but they may possibly have a role in the defence against helminths.

The mechanisms for the production and deployment of immunoglobulins are therefore well adapted to bring antibody into almost every milieu in the body where its presence may serve a useful function.

IMMUNO-DEFICIENCY AND LYMPHO-PROLIFERATIVE DISORDERS

The analysis of the functional anatomy of the immunological system has been clarified by experimental studies over the past decade, mainly on small laboratory animals. Although the critically important phase of thymic activity in man may be at an earlier prenatal period than in animals, the study of immuno-deficiency and lympho-proliferative disorders has shown that the main conclusions drawn from animal experiments are relevant to man.

So important are the immunological mechanisms for survival that it is not surprising that patients are rarely seen suffering from defects. Deficiencies of the humoral and cellular components of the immunological system may occur separately or together. Figure 12 shows the probable sites of the primary defects in the immune system for a number of clinical patterns that have been recognised.

Combined Deficiency States

A block in the development of the stem-cell leads to deficiency in both the T and B lymphocyte systems and therefore to impairment of cell-mediated hypersensitivity and of synthesis of humoral antibody (Fig. 12, lesion 1). A failure of stem-cell development at an even earlier stage leads to the additional feature of agranulocytosis although the red cells and platelets are normal. In the rare condition of ataxia telangiectasia (Fig. 12, lesion 6) there is a defect in the development of mesenchyme and the thymus fails to develop. There is also a partial failure of immunoglobulin production, particularly affecting IgA, but the reason for this is obscure.

Deficiency of Humoral Immunity

Selective primary deficiency of the B lymphocyte system occurs in sex-linked recessive hypo- or a-gammaglobulinaemia (Fig. 12, lesion 2). The lack of immunoglobulins is not absolute but the patient fails to respond to antigenic stimuli. However, cell mediated hypersensitivity and the capacity to react to a homograft are normal. It is not incompatible with survival for many years, though the patient is very susceptible to bacterial infections, particularly to pyogenic cocci.

As the different immunoglobulins have different functions, deficiencies might be expected to produce different clinical pictures. Thus IgM deficiency is possibly associated with meningococcal meningitis and lack of IgA with gastrointestinal or respiratory tract infections. In the absence of IgA the lowered resistance would permit invasion of the normally sterile upper gut by bacteria, some of which would produce decomposition of bile salts and thus affect the absorption of fat causing steatorrhoea and malabsorption.

Deficiency of Cellular Immunity

This condition is a selective primary deficiency of T lymphocytes (Fig. 12, lesions 3, 4 and 5) and is analogous to that which develops in thymectomised neonatal mice. There is severe lymphocytopenia and a predominance of reticulum cells in the lymphoid tissue. The patient's lymphocytes are unable to respond by transformation into lymphoblasts following stimulation with antigens. The failure of the patient's T lymphocytes to respond *in vitro* to PHA (p. 20) is a useful laboratory test for the detection of this type of defect. On account of the deficiency in cell mediated hypersensitivity, affected children cannot reject skin homografts and do not respond in the normal way to antigens such as monilia. Although immunoglobulin production is normal the child fails to thrive and there is wasting and diarrhoea. Candidiasis and viral infections arise and usually survival is brief.

Little is known about the role of cell-mediated immunity in acute and chronic viral infections. Its importance is emphasised by the fact that infants with thymic aplasia in whom the cell-mediated aspect is completely lacking are highly susceptible to viral infections, which usually prove fatal. It has frequently been noted that patients with agammaglobulinaemia but with normal thymic function do not suffer from severe disease in response to a number of viral infections.

The fact that there are deficient humoral antibody responses to some antigens in conditions associated with lesions at sites 3, 4 and 5 of Figure 12 exemplifies the existence of co-operation between T and B lymphocytes in relation to certain antigens as indicated in Figures 6, 8 and 9.

Secondary Immuno-deficiency

Maternal IgG is transferred across the placenta by active secretion to the fetus during the third trimester of pregnancy. Premature babies may thus have some degree of hypogammaglobulinaemia and prophylactic IgG treatment may reduce the incidence of infections. The production of immunoglobulins in the early years of life is well below that of adults and this may well explain the greatly increased susceptibility of the young to infection, particularly gastrointestinal and respiratory tract infection in relation to IgA deficiency.

Immunoglobulin deficiency may arise also in adults as a result of abnormal metabolism of serum proteins such as occurs in uraemic patients in whom susceptibility to infection is increased.

Diseases such as tuberculosis, sarcoidosis and Hodgkin's disease appear to

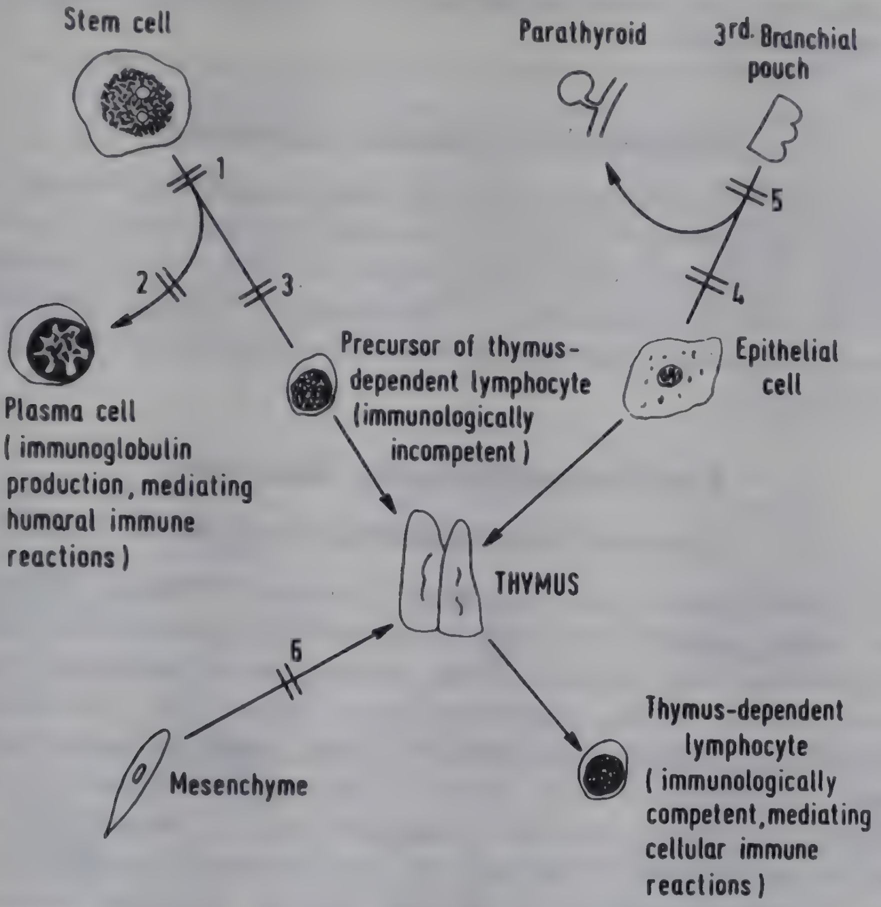

Stem cell
Parathyroid
3rd. Branchial pouch
1
2
3
4
5
Plasma cell (immunoglobulin production, mediating humoral immune reactions)
Precursor of thymus-dependent lymphocyte (immunologically incompetent)
Epithelial cell
THYMUS
6
Mesenchyme
Thymus-dependent lymphocyte (immunologically competent, mediating cellular immune reactions)

FIG. 12

The sites of developmental defects which lead to some of the immuno-deficiency syndromes observed clinically.

Site of Defect	*Clinical Syndrome*
1	Thymic hypoplasia, lymphopenia and agammaglobulinaemia (Swiss type). Autosomal recessive inheritance. Do not survive infancy.
2	Classical Bruton-type agammaglobulinaemia; normal thymus, no lymphopenia and normal cell-mediated hypersensitivity. X-linked recessive inheritance. Recurrent infection with extracellular pyogenic pathogens.
3, 4 & 5	Thymic hypoplasia and lymphopenia; normal immunoglobulins. Frequent pneumocystis, fungal or viral infections. Usually die in infancy. In 5, absence of parathyroids presenting as tetany in the newborn (Di George's syndrome).
6	Thymic hypoplasia—ataxia telangiectasia. May be part of a more widespread mesenchyme deficiency. Autosomal recessive inheritance.

(Modified from Goldstein and Mackay, *The Human Thymus*, 1969. London: Heinemann.)

depress mainly cell-mediated hypersensitivity. Drugs depressing the immune system are discussed later.

Treatment of Immuno-deficiency

Immunoglobulin injections (0·250 g/kg body weight per week, consisting mainly of IgG) can provide effective protection against severe, recurrent pyogenic infections in patients with various types of hypo- or a-gammaglobulinaemia. Recently the transplantation of fragments of human fetal thymus has been effective in replacing the cellular immune deficiency in type 5 lesions as shown in Figure 12.

Lymphoproliferative Disorders

Abnormal Immunoglobulin Synthesis

In various proliferative and neoplastic disorders, mainly of the reticulo-endothelial system, discrete components of immunoglobulins, known as myeloma or M-proteins, may appear in the plasma. In an individual patient they belong to only one of the five immunoglobulin classes IgG, IgA, IgM, IgD, or IgE and contain light chains of either K or L type. Multiple myeloma represents the malignant proliferation of a clone of plasma cells synthesising a single species of immunoglobulin, but the counterpart in the T lymphocyte population has not been so well defined. Myeloma and Waldenstrom's macroglobulinaemia (p. 755) are the most important of these conditions and when associated with diseases the proteins may be designated G-, A-, or D-myeloma or M-macroglobulins. Abnormal proteins may also occur in the urine in these disorders. Bence Jones proteinuria is found in about 50 per cent of patients with myeloma and 15 per cent of those with macroglobulinaemia. It consists of light chains only, usually dimerised (two molecules attached together as a unit).

Heavy chain disease is a very rare disorder occurring in association with rapidly progressive lymphomas. A dimer of the IgG heavy chain resembling the Fc fragment is present in the plasma and urine.

Patients with abnormal immunoglobulin synthesis have an increased susceptibility to bacterial infections and particularly to pneumonia.

TYPES OF IMMUNE REACTION AND THEIR RELATION TO HUMAN DISEASE

There are six types of immune reaction which may be harmful to the tissues (Fig. 13).

Type I— anaphylactic (immediate hypersensitivity, reagin-dependent, IgE)
Type II— cytotoxic antibody (humoral antibody, IgG, IgM)
Type III— immune complex (Arthus)
Type IV—T cell-mediated (delayed) hypersensitivity
Type V— stimulating antibody
Type VI—lymphoid (K) cell-dependent antibody-mediated (LDA) cytotoxicity.

Anaphylactic (Immediate Hypersensitivity)—Type I Reactions

In man, only IgE (reaginic) antibodies are able to produce anaphylactic Type I reactions. As these antibodies adhere strongly to tissues (and particularly to mast-cells in the tissues) they are often called tissue-sensitising antibodies. Anaphylactic phenomena are caused by antigen-antibody reaction on the surface of the mast-cell activating a series of enzymes leading to the release of certain pharmacological agents from the mast-cells (Figs 13 and 14). Individuals who have a hereditary predisposition to anaphylactic reactions are said to be atopic, as in some forms of asthma.

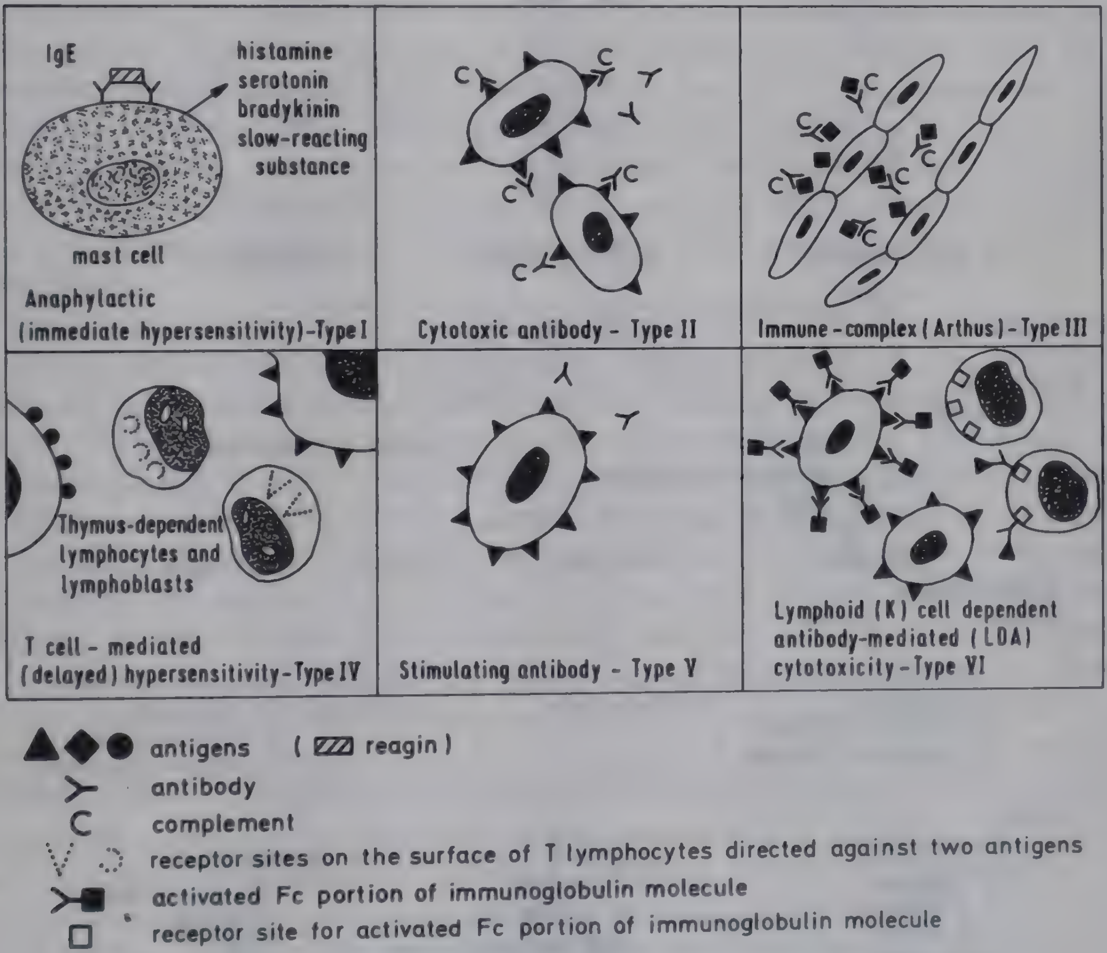

IgE
histamine
serotonin
bradykinin
slow-reacting substance
mast cell
Anaphylactic (immediate hypersensitivity)-Type I
C
Cytotoxic antibody - Type II
C
Immune-complex (Arthus)-Type III
Thymus-dependent lymphocytes and lymphoblasts
T cell - mediated (delayed) hypersensitivity-Type IV
Stimulating antibody - Type V
Lymphoid (K) cell dependent antibody-mediated (LDA) cytotoxicity-Type VI
▲◆● antigens (▨ reagin)
antibody
C complement
receptor sites on the surface of T lymphocytes directed against two antigens
activated Fc portion of immunoglobulin molecule
☐ receptor site for activated Fc portion of immunoglobulin molecule

FIG. 13

The six types of immune reaction which may be harmful to the tissues.

(From Irvine, *Proceedings of the Royal Society of Medicine*, 1974.)

Previous usage of the term anaphylaxis emphasised the clinically severe form, anaphylactic shock, but current usage refers to the underlying mechanism and not to clinical severity. In man, anaphylactic reactions are of two types depending on the portal of entry of the antigen, local or systemic. Relatively mild symptoms occur when antigen-antibody reactions occur at an exposed mucosal surface. These reactions occur most commonly to pollens or animal dander and the symptoms may be limited to rhinorrhoea and conjunctivitis (Fig. 14). However, intense bronchospasm may be produced as a result of inhalation of the antigen. Patients with asthma induced by contact with antigens in this manner have levels of IgE immunoglobulin up to six times higher than that found in patients with asthma that is not induced in this way.

A second group of more severe reactions, referred to as systemic anaphylaxis, may occur rapidly if the antigen is injected parenterally, as in the case of a drug such as penicillin, foreign sera, or the sting of an insect. This is manifested in man by bronchospasm, laryngeal oedema resulting in extreme dyspnoea and cyanosis and a marked fall in blood pressure. There may also be nausea, vomiting and diarrhoea. Systemic anaphylaxis is a potentially fatal condition if not treated promptly with adrenaline, hydrocortisone and an antihistamine.

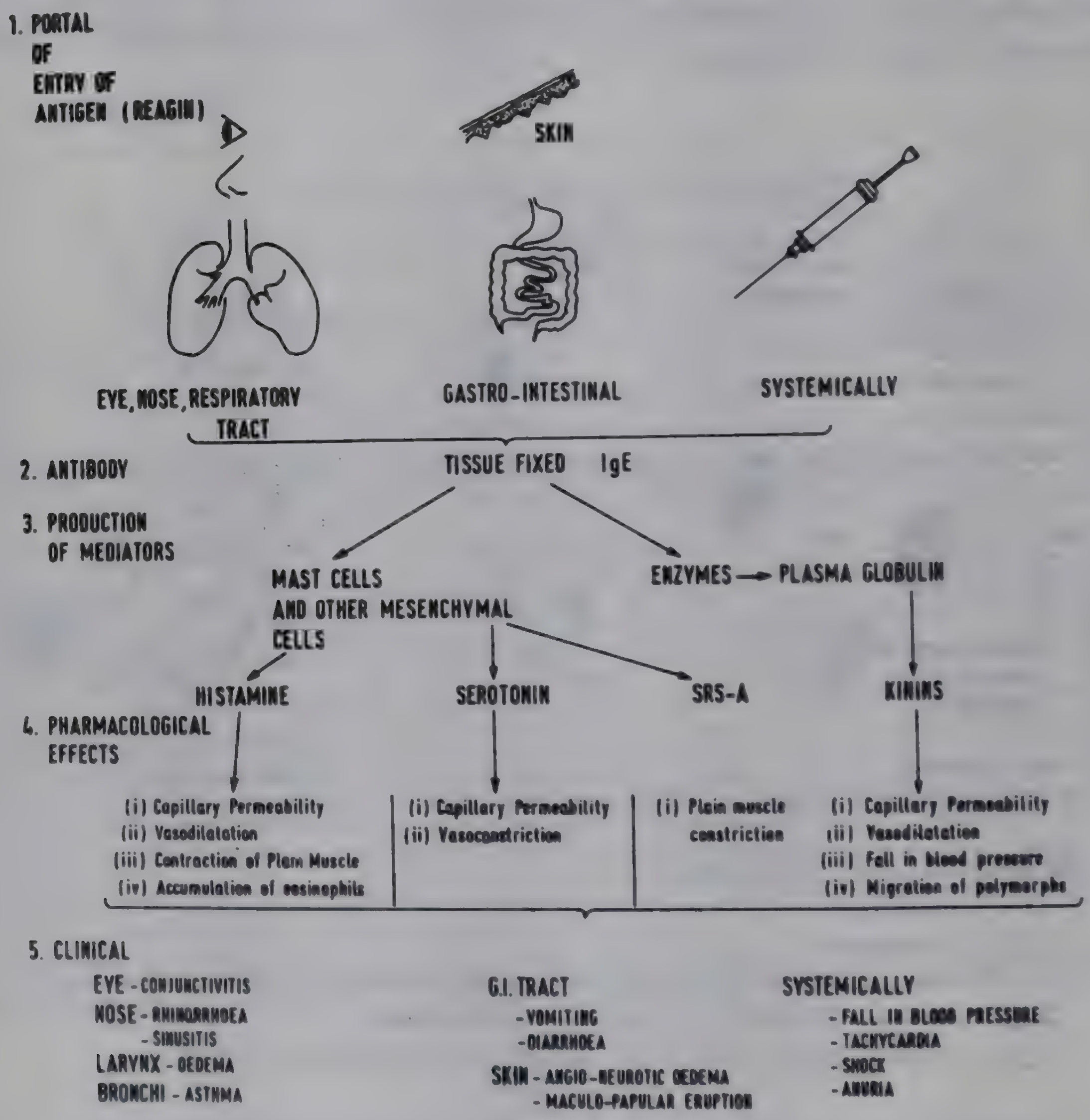

1. PORTAL OF ENTRY OF ANTIGEN (REAGIN)
SKIN
EYE, NOSE, RESPIRATORY TRACT
GASTRO-INTESTINAL
SYSTEMICALLY
2. ANTIBODY
TISSUE FIXED IgE
3. PRODUCTION OF MEDIATORS
MAST CELLS AND OTHER MESENCHYMAL CELLS
ENZYMES → PLASMA GLOBULIN
HISTAMINE
SEROTONIN
SRS-A
KININS
4. PHARMACOLOGICAL EFFECTS
(i) Capillary Permeability
(ii) Vasodilatation
(iii) Contraction of Plain Muscle
(iv) Accumulation of eosinophils
(i) Capillary Permeability
(ii) Vasoconstriction
(i) Plain muscle constriction
(i) Capillary Permeability
(ii) Vasodilatation
(iii) Fall in blood pressure
(iv) Migration of polymorphs
5. CLINICAL
EYE - CONJUNCTIVITIS
NOSE - RHINORRHOEA
- SINUSITIS
LARYNX - OEDEMA
BRONCHI - ASTHMA
G.I. TRACT
- VOMITING
- DIARRHOEA
SKIN - ANGIO-NEUROTIC OEDEMA
- MACULO-PAPULAR ERUPTION
SYSTEMICALLY
- FALL IN BLOOD PRESSURE
- TACHYCARDIA
- SHOCK
- ANURIA

FIG. 14

ANAPHYLAXIS.

(Modified from Turk, 1972.)

Cutaneous urticaria, the formation of weal and flare lesions in the skin, is an anaphylactic phenomenon which can develop as a result of absorption of antigen through the intestinal tract. Common allergens are present in strawberries, nuts, egg and shell-fish. Cutaneous urticaria often occurs alone, but may be associated with other signs of generalised anaphylaxis.

Not all urticaria is caused by an immune reaction. It is known that the pharmacological agents which cause urticaria can be released by other means, especially physical agents such as trauma or cold. Most of the reactions found in anaphylaxis can be attributed to the release or activation of pharmacological agents. Of these only four have so far been recognised. They are histamine, slow reacting substance-A, serotonin (5H-T) and a group of related agents known as the plasma kinins (Fig. 14).

The plasma kinins—bradykinin and kallidin—are simple peptides formed from plasma globulins by the enzymes, kallikrein, plasmin or trypsin. They cause increased capillary permeability, vasodilation and a fall in blood pressure. Bradykinin produces pain when injected into man. Another effect is to cause polymorphonuclear leucocytes to migrate from blood vessels and accumulate in the tissues (chemotaxis). Once they are formed the kinins are rapidly broken down by kininases present in the blood. Thus their accumulation at any site is controlled.

If serum containing reaginic antibody (IgE) is injected intradermally that area will remain responsive to the appropriate antigen (reagin) for over 48 hours. This is the fundamental basis of the Prausnitz-Kustner reaction for the demonstration of the presence of these reaginic antibodies in man. This effect was first demonstrated in 1921 when Dr Kustner, who was hypersensitive to cooked fish, conferred his sensitivity upon a small test area of the skin of Dr Prausnitz who previously did not suffer any ill-effects from fish. About 24 hours after the transfer, the antigen was pricked into the area of skin which had been sensitised. Within 20 minutes a typical weal and flare similar to that produced by histamine developed in the skin. Injections of human serum carry a strong risk of transferring serum hepatitis and should no longer be undertaken. An *in vitro* method that has been used is to link the antigen (reagin) to red cells and then react the antigen-red cell complex with the test serum. If the test serum contains IgE antibody for that reagin then the red cells will become coated with it and can be agglutinated by anti-sera prepared specifically against the IgE immunoglobulin. This technique should eventually prove suitable for routine *in vitro* testing with a wide range of antigens (reagins) for this type of hypersensitivity.

Cytotoxic (Humoral Antibody)—Type II Reactions

The clearest example of a Type II reaction as a cause of disease occurs in autoimmune haemolytic anaemia; red cell destruction is the result of absorption of autoantibodies on to the cell surface and this can be demonstrated *in vitro* by the antiglobulin (Coombs') test (p. 740). When anti-human globulin is added to a suspension of the patient's red cells that have antibody on their surfaces, agglutination of the cells occurs. *In vivo*, the altered or damaged red cells are destroyed by the reticulo-endothelial system in the spleen or liver. Both IgG and IgM antibodies have been implicated.

Circulating antibodies reacting *in vitro* with other tissue components are a common occurrence in a wide range of diseases in man, but their role in causing the corresponding disease is less clear. Another example of IgG antibodies being directly pathogenic is antibody to glomerular basement membrane in certain types of experimental glomerulonephritis in animals and in a rare type of glomerulonephritis in man associated with haemoptysis (Goodpasture's syndrome, p. 592). In these forms of glomerulonephritis, antibody to the glomerular basement membrane is laid down in a linear fashion along the basement membrane. This can be demonstrated by immunofluorescence or by electron microscopy. Infusion of such antibodies into experimental animals rapidly induces glomerulonephritis and this mechanism may result in damage to a kidney transplant in a patient whose own kidneys had previously been destroyed by glomerulonephritis.

In other instances, current evidence would suggest that IgG antibodies may have only a weakly pathogenic effect. Thus, the occurrence of intrinsic factor antibodies in the circulation of a patient shows a strong correlation with Addisonian pernicious anaemia, but the role of the antibody in causing the gastric atrophy characteristic of this condition is not clear. For example, pernicious anaemia may occur in patients with marked hypogammaglobulinaemia. However, antibody reactive with the vitamin B_{12} binding site of intrinsic factor has been shown to be present in the gastric juice of some patients with pernicious anaemia: it may block the action of any remaining secretion of intrinsic factor with consequent malabsorption of vitamin B_{12}.

There are circumstances in which IgG antibodies may be pathogenic only when combined with cell-mediated hypersensitivity or other forms of tissue damage. Thus in experimental orchitis in guinea-pigs neither circulating antibody nor hypersensitivity alone is sufficient to produce lesions and both types of immune reaction are necessary. Again complement-fixing IgG antibodies to thyroid secretory epithelium are a frequent occurrence in autoimmune thyroid disease but they seem to have little or no pathogenic role by themselves. These antibodies can be transmitted across the placenta with no evidence of damage to the fetal thyroid. Although at least one of these antibodies can bring about rapid destruction of trypsinised human thyroid cells *in vitro* in the presence of complement, *in vivo* it seems to have difficulty in reaching the intracellular antigens in the absence of some other damaging agent.

Finally, in other situations, antibodies detectable in the serum and often useful diagnostically, seem to have no discernible pathogenic role when acting on their own. For example, antibody to thyroglobulin is harmless to thyroid cells in tissue culture and infusion into animals produces at most a weak granulomatous reaction in the thyroid. A second example is the mitochondrial antibodies with no tissue specificity which occur in patients with active chronic hepatitis, in primary biliary cirrhosis and in cryptogenic cirrhosis. However, antibody to thyroglobulin may play an important role in pathogenesis when part of a type VI reaction (p. 36).

In summary, antibodies detectable in the circulation or produced locally in certain tissues by infiltrating plasma cells may be directly responsible for certain diseases, while in other diseases such antibodies, although abundantly present and useful in diagnosis, do not seem to have a direct role on their own account.

Diagnostic methods. Those most widely used for the detection of antibodies in the serum are:

THE INDIRECT IMMUNOFLUORESCENCE TECHNIQUE. This method is used to detect autoantibodies to nuclei (antinuclear factors), to thyroid cytoplasm, to the cytoplasm of gastric parietal cells, to the cytoplasm of the cells of the adrenal cortex and to glomerular basement membrane.

COMPLEMENT FIXATION TESTS. Certain antigen-antibody reactions fix complement and the occurrence of such a reaction *in vitro* can be detected by determining whether complement, which had been added in a critical amount, is still present in the free form. An indicator system is used consisting of sheep red cells coated with horse or rabbit antibodies against the red cells. If complement has been fixed before the addition of the indicator system, it is no longer available to permit lysis of the sheep red cells. This technique forms the basis of the Wassermann reaction for syphilis, and the gonococcal complement fixation test; it is also used in the demonstration of antibodies against certain viruses and also for thyroid and gastric autoantibodies in serum.

PRECIPITATION TEST. This is used, for example, in the detection of antibodies to thyroglobulin in the differential diagnosis of thyroid disorders.

TANNED RED CELL OR LATEX PARTICLE AGGLUTINATION. Sheep red cells are treated with tannic acid so that they can be coated with antigens (e.g. thyroglobulin). In the presence of the corresponding antibody the cells undergo agglutination. This provides a very sensitive and semi-quantitative method for the detection of certain serum antibodies, e.g. to thyroglobulin. Latex particles coated with human γ-globulin are used to detect the presence of the rheumatoid factor in patients' serum.

Immune Complex (Arthus)—Type III Reactions

Immune complex reactions are induced by deposition of antigen-antibody complexes in the tissues, causing an inflammatory reaction via mediators such as complement. Complement consists of a variety of proteins some of which are proteolytic enzymes. These are activated in turn and bring about an amplification of the immune process as shown in Figure 15. Thus the deposition of immune complexes causes the activation of complement which results in a polymorphonuclear inflammatory response and also damage to the cell membranes of adjacent tissues. Hydrolytic enzymes released from the granules of the leucocytes also contribute to the irreversible vascular damage which is the hallmark of this type of immune reaction.

The immune complex reaction can be induced in man by the intradermal injection of antigens if there is a high level of circulating IgG antibodies, for example by the intradermal injection of fungal antigens in pulmonary aspergillosis (p. 372) and of thermophilic actinomycetes in patients with the disease 'farmer's lung' (p. 383). Immune complex reactions in man are red and oedematous reaching maximum intensity between 4 and 12 hours after intradermal injection.

The systemic syndrome known as chronic serum sickness is based on an immune complex reaction and can be produced by a wide range of different antigens, such as antitetanus serum and especially drugs such as penicillin, streptomycin, sulphonamides and the thiouracils. It consists of skin rashes, fever, joint pains and often swelling of the regional lymph nodes. The duration of symptoms varies greatly. The illness is seldom serious, though it may give rise to much discomfort.

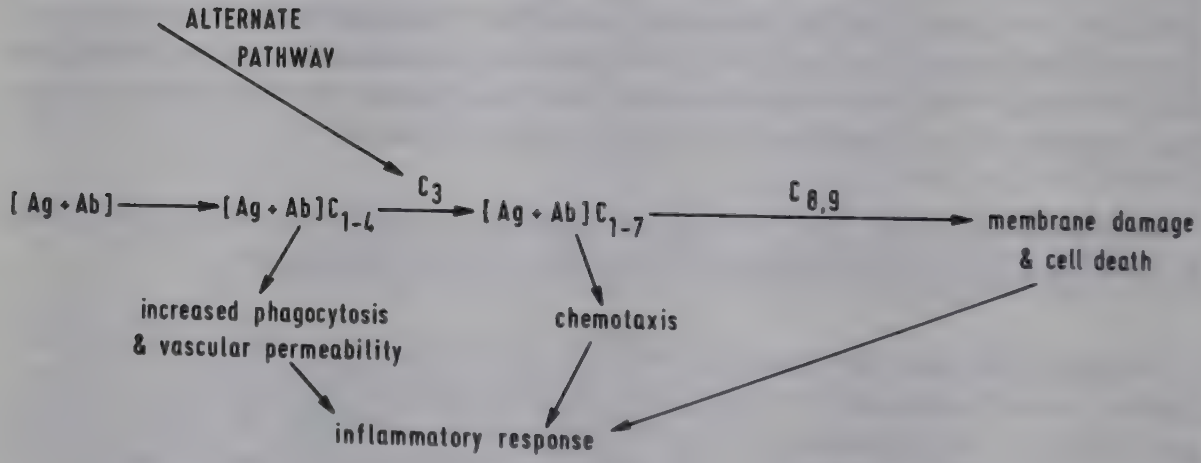


Fig. 15

The Role of Complement in Immune-complex Reactions

(Ag+Ab) = antigen+antibody immune complex deposited in tissue in the presence of moderate antigen excess.
C = complement.

Glomerulonephritis can also be caused by an immune complex reaction. Thus, in the clinical entity of glomerulonephritis, there are at least two immune pathogenic mechanisms and, in all probability, numerous aetiological factors capable of initiating each. As described on page 32, in glomerulonephritis produced by a Type II immune reaction the patient or experimental animal produces or is given antibodies reactive with their own glomerular basement membranes. In glomerulonephritis produced by an immune complex reaction the specificity of the antibodies is irrelevant; what is important is that antigen-antibody complexes of appropriate size are present in the circulation and are deposited in the glomerular capillary walls.

The only property of antigen-antibody complexes presently known to affect the localisation in vessels is size. Small complexes in great antigen excess tend to remain in the circulation whereas frank precipitates formed at equivalence or at antibody excess are rapidly taken up and disposed of by phagocytes. The intermediate-sized complexes formed in moderate antigen excess are still soluble but large enough to react with complement and are the most likely to be deposited in vessel walls and so induce inflammation. The vessel walls of the renal glomeruli are particularly vulnerable. Morphologically the trapped antigen-antibody complexes appear under the electron microscope as heaped-up lesions on the epithelial surface of the glomerular basement membrane. The circulating level of the third component of complement (C3) is reduced in glomerulonephritis due to immune complex disease.

Immune complex reactions may or may not be related to autoimmunity. The antigen involved may be foreign to the body or it may be autogenous. Thus, poststreptococcal proliferative glomerulonephritis, at least as seen in children, is caused by the deposition of circulating non-glomerular antigen-antibody complexes. The best example of an autogenous immune complex reaction causing glomerulonephritis in man is that occurring in systemic lupus erythematosus. It is associated with the formation of antinuclear antibodies (particularly to DNA) and the deposition of these antibodies, nuclear antigens and complement in the renal glomerulus.

Cell-mediated (Delayed) Hypersensitivity—Type IV Reactions

Type IV reactions are those mediated by T lymphocytes and in which free antibody plays no part. They are characteristically induced by infectious agents which are predominantly intracellular in the infected host, e.g. many viral infections such as measles, smallpox, herpes and some bacterial infections (tuberculosis, brucellosis, pertussis, and syphilis). The classical example of this reaction is the tuberculin response, in which the sensitised individual produces an inflammatory, indurated area consisting mainly of mononuclear cells and which gradually appears over 18 to 48 hours. The homograft reaction is believed to be predominantly produced by cell-mediated hypersensitivity in which the thymus-dependent lymphoblasts and lymphocytes (Figs 13 and 16) are the main effector cells.

Type IV reactions can also occur by skin contact with a variety of substances ranging from nickel in brassière straps to drugs including penicillin. These substances are not themselves antigenic but become antigenic by co-valent binding to proteins in the skin. The hypersensitivity of the skin is generalised and may be detected by the application of a small patch test containing the substance anywhere on the body. Transfer of contact dermatitis has been achieved in animals and in man with lymphocytes from the thoracic duct and spleen. The clinical features of contact dermatitis include redness, swelling, vesiculation, scaling and exudation of fluid.

AUTOIMMUNE DISEASE. Evidence suggesting the importance of cell-mediated hypersensitivity as a cause of autoimmune disease can be summarised as follows:

1. The histology of the affected organs shows lymphocytic infiltration and

atrophy, e.g. in Hashimoto thyroiditis, atrophic gastritis of Addisonian pernicious anaemia and idiopathic (autoimmune) adrenal failure.

2. Similar histological changes can be produced in animals by sterile methods that cause cell-mediated hypersensitivity in relation to the tissue antigens used for immunisation, e.g. injection into the foot pads of tissue antigen emulsified in Freund's adjuvant (p. 22).

3. When such diseases have been induced immunologically in experimental animals they can be transferred to normal animals by means of lymphocytes alone.

4. Positive *in vitro* tests supposedly for cell-mediated hypersensitivity have been obtained with the lymphocytes from the peripheral blood of patients or of experimental animals with certain autoimmune diseases. These tests include the leucocyte migration inhibition test, transformation and cytotoxicity tests. As shown in Figure 6, when T lymphocytes that have been sensitised to a specific antigen come into contact with that antigen, the lymphocytes undergo blast transformation (which can be quantitated by measuring the uptake of tritiated thymidine) and among the lymphokines released is one that inhibits the migration of macrophage in tissue culture and supposedly *in vivo*. Cytotoxicity by lymphocytes is quantitated by measuring the release of isotopes from labelled chicken or sheep red cells coated with the appropriate antigen.

It must be emphasised, however, that the lymphocytes or lymphoid cells infiltrating affected tissues may be T, B or K cells and that until cell marker studies have been done on the affected tissues no statement can be made concerning the predominant cell type.

Stimulating Antibody—Type V Reaction

Certain IgG antibodies, and the long-acting thyroid stimulator (LATS) is the best example, have the ability to stimulate their target cells rather than to inhibit or kill them. Human specific LATS is a likely cause of thyrotoxicosis in some cases and its transfer across the placenta is the most probable explanation for neonatal hyperthyroidism.

Lymphoid (K) cell-dependent Antibody-mediated (LDA) Cytotoxicity—Type VI Reaction

In this reaction non-sensitised lymphocytes belonging to neither the T nor B classes and representing not more than 10 per cent of the lymphocytes in the peripheral blood, acquire specific cytotoxicity by reacting with the activated Fc portion of an antibody molecule complexed with antigen on the surface of the target cells (Fig. 13). It also appears that this type of lymphocyte may acquire licence to kill specific cells by reacting with free antigen-antibody complexes in the presence of antibody excess. When such a lymphocyte encounters the corresponding antigen on the surface of tissue cells it is cytotoxic. This mechanism has been shown to be operative in autoimmune thyroid disease and may be important in cancer rejection. Should immune complexes be produced in the presence of excess antigen, there would be no free combining sites left on the antibody moiety to react with antigen on tissue surfaces so that this type of lymphoid cell would be ineffective (blocked).

Immune mechanisms may simply be part of a chain of events that leads to the final end product, the clinical manifestation of disease (Fig. 16). Experimental myasthenia gravis is an example. A thymitis can be induced by immunisation using thymus or skeletal muscle in Freund's adjuvant. Humoral antibodies reactive with A or I bands of skeletal muscle and myoid cells in the thymus are produced and also type IV reactions to extracts of skeletal muscle and presumably of the thymus. As a result of the thymitis which is produced, a substance

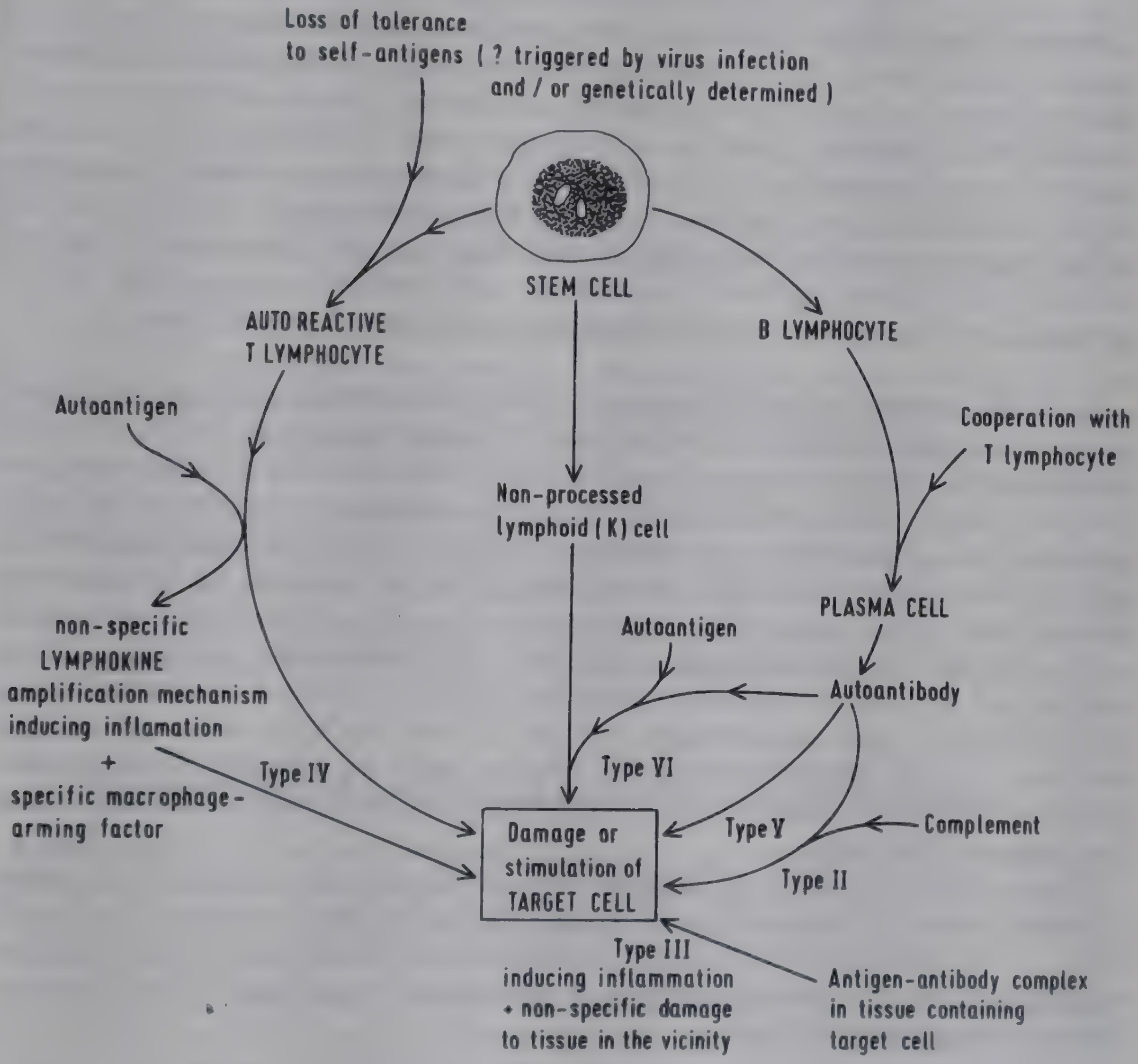


FIG. 16

Diagram representing the interactions of immune mechanisms types II-VI in the production of autoimmune disease. The different mechanisms may have greater importance in some diseases than in others. Thus type II reactions are predominant in autoimmune haemolytic anaemia, while types II, IV and VI are predominant in Hashimoto's thyroiditis, and possibly type V in thyrotoxicosis.

The lymphokine and complement systems may be regarded as non-specific amplification mechanisms in order to boost the effect of a small number of specifically sensitised cells or antibody interacting with the antigen at the target site. Specific macrophage arming factor may be regarded as a specific amplification mechanism.

is released that is not antibody but which impairs neuromuscular transmission in a manner characteristic of myasthenia gravis.

Why should autoimmune reactions occur?

Sequestrated Antigen. There are some antigens, such as those of the lens of the eye, that do not normally come into contact with the immunological system so that there has been no opportunity for immunological tolerance or self-recognition to develop. Injury to an eye may result in the escape of antigen with antibody formation as a physiological consequence and lead to immunological damage to the other eye (sympathetic ophthalmia). A further example of this is sperm, which if extravasated following unilateral blockage of the vas deferens may induce antibody formation and contribute to sterility. Sperm antibodies may also be produced following vasectomy in normal men.

Defect in Immunological Tolerance. A defect in immunological tolerance may occur either spontaneously or be induced by some exogenous factor. It could be argued that the intricate and precise system whereby foreign substances are normally clearly distinguished from the body's own constituents must be liable to breakdown so that errors are made as to what is part of the body and what is not. On the present evidence it would seem that the bulk of the autoimmune diseases may come under this category. At one end of the spectrum are the organ-specific, but interrelated, disorders of autoimmune thyroid disease, Addisonian pernicious anaemia, idiopathic Addison's disease, idiopathic hypoparathyroidism and autoimmune ovarian failure. At the other end of the spectrum are the non-organ-specific diseases such as systemic lupus erythematosus. Sjögren's disease and the autoimmune liver diseases perhaps come somewhere in between.

There is some evidence to suggest that, at least in the organ-specific autoimmune diseases, there is a loss of T cell control on the function of the B cells (Fig. 9). The claim that T cell function diminishes with age provides an attractive explanation for the rising incidence of subclinical organ-specific autoimmune disease with advancing years.

Infection. In the hypersensitive host, invading micro-organisms may share antigen with certain of the host's tissues and induce the formation of antibodies which cross-react with these tissues. Possibly this may be an effect of antigen dosage. Thus the sharing of antigen between some Group A β-haemolytic streptococci and the heart may be relevant to rheumatic carditis. Likewise, the sharing of antigen between *Esch. coli* O14 and colon epithelium may be relevant to the pathogenesis of ulcerative colitis.

Drugs. Some drugs such as methyldopa seem to alter the immunological system so that antibodies develop that are reactive with red cells producing a positive Coombs' test and a haemolytic anaemia which is reversible on withdrawal of the drug. Alternatively it is possible that methyldopa in some way unmasks antigens present on the erythrocyte surface which do not under normal conditions stimulate antibody production. Other drugs such as procainamide are associated with the development of antinuclear antibodies.

Genetic Factors. When the breakdown of immunological tolerance seems to be spontaneous one asks whether it is genetically determined, whether it occurs by spontaneous mutation or whether it might be induced by some agent such as a virus that has so far escaped recognition at least in the human situation. It is known that there is a genetic factor operating in the autoimmune diseases of disordered immunological tolerance, but the exact mode of inheritance escapes clear definition. A characteristic feature of the autoimmune diseases is that the autoantibodies are formed continually, at least over a period of years. By contrast, if a tissue is damaged by some other means—such as occurs in myocardial infarction, burns, etc.—in general the corresponding antibodies appear only temporarily.

The genetic factor could operate as a built-in defect in the immune system so that, usually later rather than sooner, tolerance breaks down according to a certain pattern. Alternatively, what may be genetically determined is susceptibility to an exogenous agent such as a virus, for which there is some evidence in a special strain of mice. However, there is as yet no convincing evidence that genetic susceptibility to a virus infection is the basis of autoimmune diseases in man. Whether or not there is an exogenous factor operating in man is a question that remains unanswered. Also unanswered is why immunological tolerance should break down according to certain patterns that clinicians recognise as interrelated diseases in which immune mechanisms seem to play an important part.

Suppression of Immune Reactions or of their Effects

Antihistamines. When anaphylaxis presents as an acute clinical problem the immediate aim is to give drugs which antagonise the effects of the mediators. These antagonists are the antihistamines and various drugs which have opposite actions to the mediators.

The antihistamines occupy the same tissue receptors as histamine without providing any stimulus to the effector cells. In man, the intravenous injection of the antihistamine, chlorpheniramine, quickly produces adequate tissue concentrations. The weal, the erythema and the itch of acute urticaria are reduced but there is no consistent improvement in lung function in acute bronchial asthma. The failure of the antihistamines to relieve airways obstruction caused by an anaphylactic reaction has been attributed to high concentrations of histamine close to the smooth muscle cells. It may also be due to the presence of other mediators of the anaphylactic response. Bradykinin is rapidly inactivated in plasma by a kininase but its effects are not inhibited by antihistamines. No specific antagonists of bradykinin or SRS-A are known, although salicylates have been shown to suppress experimental anaphylaxis in guinea-pigs.

Disodium Cromoglycate. This compound (p. 380) is believed to inhibit the release of the mediators following the interaction of antigens (reagins) with IgE antibodies. It is partially effective in preventing the induction of asthma by specific antigens. If inhaled by an asthmatic subject before exposure to the antigen, protection may last for several hours, but if given after exposure to the antigen it has little effect.

Adrenaline and Related Drugs. In clinical emergencies drugs which act by producing effects which oppose the mediators are more effective than the antihistamines. Adrenaline, isoprenaline and aminophylline are efficient bronchodilators in acute bronchial asthma. Adrenaline also produces constriction of the arterioles in the skin and splanchnic area. Vascular permeability and oedema are reduced. Urticaria is relieved and where oedema threatens the airway, the risk of asphyxia is lessened. Despite their effectiveness these non-specific antagonists have serious disadvantages. They are antagonists in their own right, acting on receptors which differ from those occupied by the mediators, and their effects never precisely counteract those of the mediators. The dose of a sympathomimetic amine which relieves airways obstruction may produce tachycardia and palpitations even when the amine is administered as an inhaled aerosol. Salbutamol does not have these disadvantages as it is more specific in its actions on β-adrenergic receptors in the bronchi.

Corticosteroids. Hydrocortisone or prednisolone produce improvement in status asthmaticus in a few hours. The mechanism is not known but is probably related to their anti-inflammatory actions and not to selective interference with any particular stage in the development of the anaphylactic response. Their use in Types II, III and IV immune reactions is discussed below.

Hyposensitisation. Anaphylactic individuals can be made less sensitive by multiple subcutaneous injections of antigen. Pollen antigens can be used to prevent the development of hay fever and asthma in some patients. Up to 50 subcutaneous injections may be given, gradually increasing the dose of antigen. Another technique is to suspend the antigen in an oily base. As a result of slower absorption the patient develops IgG antibodies against the antigen over a longer period. These antibodies have a higher avidity for the antigen than do IgE antibodies and are able to compete successfully for the antigen sites on the pollen, fragment of insect or whatever has induced the anaphylactic response. As reactions with the IgG antibodies do not take place at cell surfaces, anaphylactic phenomena are not produced. The reactions with the IgG antibodies do not have any harmful effect as the amount of IgG antibodies produced is not sufficient to cause an immune-complex (Type III) reaction. In this context the IgG antibodies are referred to as blocking antibodies.

Cytotoxic Drugs. The production of immunoglobulins and the cellular immune response are dependent upon the division of lymphoid cells. Drugs which interfere with dividing cells are therefore all potentially immunosuppressive. Such drugs were originally developed as anti-tumour agents and are generally referred to as cytotoxic drugs. Of these azathioprine, cyclophosphamide and methotrexate have been used as immunosuppressive drugs. Their side-effects of bone-marrow suppression and depletion of the intestinal epithelium are to be expected. In organ transplantation the use of azathioprine has become almost universal and it is under trial in the treatment of other diseases such as systemic lupus erythematosus, the autoimmune liver diseases and ulcerative colitis. When used in daily maintenance doses of 3 mg/kg body weight, azathioprine does not produce serious side-effects if renal function is satisfactory.

Anti-lymphocyte Serum. This substance, or a semi-purified globulin containing the active fraction, is a potent agent for the suppression of cell-mediated immunity. It is prepared by immunising another species, usually the horse, with human lymphocytes. The precise mode of action is debatable but it interferes with the function of T lymphocytes while not affecting antibody formation to previously encountered antigens. Its main application has been in relation to organ transplantation, but it may have some place in the more serious autoimmune diseases. The major side-effects are the development of anaphylactic reactions to the injection of serum of another species and the development of antibodies to the anti-lymphocyte serum with deposition of immune complexes in the kidney and consequent renal damage. A further possible hazard, shared by other immunosuppressive agents, is an increased incidence of malignant tumours, such as lymphomas, on account of the suppression of immunological surveillance of the body tissues which is part of the normal mechanism for the control of spontaneous tumours (see below).

Anti-D Immunoglobulin. The clearest example of interference with a specific immune response is the use of human anti-D immunoglobulin to prevent haemolytic disease of the newborn (p. 738). This specific human antibody preparation is derived mainly from the immunisation of Rh-negative male volunteers. Given by intramuscular injection to a Rh-negative woman bearing a Rh-positive child within 72 hours of the child's birth, it will prevent the mother from being primarily sensitised to the blood group D antigen and thus will also prevent the development of haemolytic disease in a child of a subsequent pregnancy. The patient develops a specific tolerance to the Rh antigen by means of the passive transfer of the specific antibody. The antibody either combines with the Rh antigen which has recently entered the mother's circulation during parturition or it effectively competes with antibody receptor sites on the lymphocyte and so prevents lymphocyte activation and therefore antibody formation. This principle may be applicable to transplantation immunology.

'Anti-Inflammatory Agents'. Drugs which interfere with the unwanted consequences of Types II, III and IV immune reactions include the corticosteroids and, to a lesser extent, salicylates. The corticosteroids may also partially suppress the development of immune responses, but when used in high dosage they have serious side-effects. Use is therefore being made of other 'anti-flammatory' drugs such as indomethacin or phenylbutazone, sometimes in combination with a cytotoxic drug.

Thymectomy. The only human autoimmune disease for which thymectomy is regularly performed is myasthenia gravis. It has its best effect in females with myasthenia gravis but no thymoma, particularly when the duration of the disease has been short. This is compatible with the experimental studies described (pp. 19-20). Thymectomy has also been successful in infants with autoimmune haemolytic anaemia when other methods have failed. Apart from myasthenia gravis, thymectomy has not been helpful in relation to autoimmunity in adults, where it has been tried for example in systemic lupus erythematosus. Thymectomy as a treatment for autoimmune diseases other than myasthenia gravis may be effective only in childhood when the influence of the thymus on the immunological system is particularly important.

Cancer Immunology. Cancer cells lose some of the normal tissue specific antigens and appear to gain some tumour associated antigens which were not previously present in the cells from which they were derived. It is believed that the process of immunological surveillance destroys many early cancers by virtue of the recognition by the normal immune system of the 'foreignness' of tumour associated antigens. A correlation is recognised between failure of the immune system—either naturally occurring with increasing age or as primary immunodeficiency disease or induced by immunosuppression—and the incidence of cancer. An interesting line of future research and possible clinical application is the augmentation of the normal immune response so as to help ablate malignant growth after the bulk of the tumour has been removed or killed by conventional means. Immunisation with BCG and allogeneic irradiated malignant cells has already been shown to be beneficial in acute myeloid leukaemia.

There is exciting recent work which suggests that, in the presence of continued antigenic stimulation, macrophages, previously coated with specific macrophage arming factor, may become activated so that they are cytolytic to rapidly dividing (e.g. malignant) as opposed to normal cells. There is also increasing evidence which suggests that antigens from malignant tumours are released into the circulation in excess of the amount of antibody produced against the tumour; this situation of antigen excess would block type VI cytotoxic reactions and thereby overcome one of the body's defences. It is also likely that non-immunological toxic factors may induce a state of relative immunodeficiency in cancer patients.

W. J. IRVINE.

Further reading:

Irvine, W. J. (1973). In *Companion to Medical Studies*, vol. 2, chap. 23. Oxford: Blackwell.

Roitt, I. M. (1972). *Essential Immunology*. Oxford: Blackwell.

Turk, J. L. (1972). *Immunology in Clinical Medicine*. London: Heinemann.

Weir, D. M. (1973). *Immunology for Undergraduates*, 3rd ed. Edinburgh and London: Churchill Livingstone.

More detailed texts:

Gell, P. G. H., Coombs, R. R. A. & Lachman, P. J. (1974). *Clinical Aspects of Immunology*. Oxford: Blackwell.

Humphrey, J. W. & White, R. G. (1970). *Immunology for Students of Medicine*. Oxford: Blackwell.

Infection and Disease

THE life and health of human beings, animals and plants are constantly threatened by parasites, particularly by micro-organisms—protozoa, fungi, bacteria and viruses, which after invasion of the tissues may produce infectious disease. In numerical terms this is the most important group of maladies affecting the human race.

The great majority of these pathogenic micro-organisms have now been identified and their biological characters studied. Most important has been the building up of epidemiological data regarding their sources and modes of spread; details are known of their pathogenic mechanisms and the host's defence reactions and, perhaps of greatest impact, successful methods have been developed which can inhibit and kill these organisms both inside and outside the host. This knowledge has allowed more effective control of most infectious diseases through the application of preventive measures (public health), the raising of resistance of the host (immunity) and the effective treatment of individuals suffering from infection (specific antimicrobial measures). Thus in areas where the full effect of modern medicine is felt, many of the infectious diseases, which previously were frequently responsible for a high mortality, have almost vanished, e.g. typhoid and smallpox. While the mortality from infectious diseases is now low in Britain the morbidity remains high, and is responsible for much ill-health and absenteeism.

The control of infection cannot be fully effective without a knowledge of the nature of the infecting organism, the epidemiological factors involved in the source and spread of infection and the nature of the host's defences. A brief discussion of these follows, and thereafter the general features of infection and its prevention are considered.

NATURE OF THE MICRO-ORGANISM

Micro-organisms may be *saprophytic*, living an independent existence in soil and water, or in waste and dead material, and generally such organisms do not produce disease in man. There are exceptions, for example the toxins of *Clostridium botulinum* which may contaminate prepared foodstuffs and lead to toxaemia and even death. Bacteria normally saprophytic such as *Pseudomonas*, may be *opportunist pathogens* when they invade the tissues under exceptional conditions; such circumstances occur more frequently in hospital when the organism may survive even in antiseptics and be introduced into wounds or body cavities. Disturbance of the commensal flora of the body by antimicrobial agents may also allow the establishment of opportunist pathogens, such as *Candida* which can lead to thrush infection.

In contrast other micro-organisms are parasites living in close association with a host; some are highly adapted to local conditions on the surfaces of the body and are best described as *commensals* which under certain conditions may invade the tissues; other parasites play a more definite part in disease and are described as *pathogens*. There is of course no hard and fast dividing line and many pathogens exist in an apparently quiescent role as commensals.

Variation in Micro-organisms

In common with other living creatures micro-organisms adapt to their environment by changes in their genetic structure which result in variation of characters in a proportion of their progeny. These changes become apparent in a relatively short time because of the high rate of reproduction of micro-organisms so that differences affecting a large proportion of a population producing an infection may be noticeable during the period of the disease. When the characters affected by these genetic changes are related to pathogenicity, virulence and resistance to antimicrobial agents, they are of particular importance in medicine and in the management of individual patients.

Among bacteria there are a number of ways in which changes in genetic structure occur. Firstly, accidental addition, omission or alteration may occur in the structure of the chromosome during cell division (*spontaneous mutation*). Secondly, genetic material may be directly transferred from one cell to another and confer a character of the donor on the recipient cell (*transformation*), e.g. the change in type which takes place in *Streptococcus pneumoniae*; a similar mechanism is believed to cause changes in susceptibility to tetracycline in some strains of *Streptococcus pyogenes*. Thirdly, *transduction* is a somewhat similar mechanism which results in the genetic character being carried from the donor cell to the recipient by a bacteriophage particle and introduced either into the bacterial chromosome or into the cell merely as an extra chromosomal particle. Resistance due to the production of penicillinase is acquired by penicillin sensitive *Staphylococcus pyogenes* in this way, as also is the toxigenicity of avirulent strains of *Corynebacterium diphtheriae*.

Finally, *conjugation* allows the direct transfer of genetic material between donor and recipient cells. So far this has been described only for the Gram-negative coliform bacilli and related species. Sexual conjugation is a relatively rare occurrence in bacteria and usually involves the transfer of part of the single bacterial chromosome. In certain situations some donor cells may acquire a transfer factor which increases the rate of conjugation and allows the transfer from cell to cell of extra chromosomal genetic material. When this contains characters conferring antibiotic resistance the term *resistance transfer factor* is used and its importance is in the relatively high rate of transfer to sensitive cells (*infectious resistance*) and in the fact that susceptibility to more than one antibiotic may be simultaneously involved. This mechanism is believed to be of great importance in the rapid changes in resistance which may take place among Gram-negative bacilli such as *Escherichia coli* and *Shigella*.

Whichever mechanism is involved in creating a genetic change, the affected progeny constitute cells with a differing potentiality for growth and survival. Various *selective factors* in the environment may favour the growth and spread of these genotypes and when this occurs their numbers will increase and they will become apparent. Antibiotics can act as selective factors for bacteria resistant to them and encourage the appearance of antibiotic resistant strains. Thus the occurrence of antibiotic-resistant strains of bacteria has tended to increase in relation to the amount of usage of antibiotics and chemotherapeutic agents, particularly in closed environments such as hospitals.

EPIDEMIOLOGY OF INFECTION

Source of Infection

The *source* of infection is the site where the pathogen is growing and multiplying. Infection in man may be *autogenous* where the source is the patient himself, or *exogenous* where it is from some other source such as a different person. Infection which is autogenous may result from recent colonisation of the host following contamination from an exogenous source. This frequently occurs in hospital where pathogenic staphylococci from the environment may colonise staff and patients and then cause infection in some of these persons.

Human Sources

Pathogenic micro-organisms are usually species specific and therefore the most common sources of infection in man are other persons. These human sources are, (*a*) patients who are in the incubation period, course or convalescent stage of infection, and (*b*) *carriers* who are healthy but harbour pathogens which can be transmitted to others. Carriers may never have suffered from clinical infection (healthy carriers) or may be convalescent after clinical recovery (convalescent carriers), and, as after typhoid fever, may continue to excrete the causative organism for many years.

Animal-borne Infection

The animal vector may be intimately concerned in the cycle of disease, e.g. the mosquito in malaria and yellow fever; many other epidemic infections due to viruses, rickettsiae, bacteria and protozoa are spread by blood-sucking insects. Other animals may be the natural host of infections which can be spread to man (zoonoses), e.g. brucellosis from milk cows or goats, glanders from horses and salmonellosis from birds or rodents.

Inanimate Sources

A few infections arise from non-living sources. Certain saprophytes may act as opportunists and the soil is the apparent source of some bacteria (*Cl. botulinum* and *Cl. tetani*) which cause human disease although ultimately many of these species are derived from animals. Fungi such as *Coccidioides* and *Blastomyces*, normally saprophytes in the soil, may produce systemic infection. An increasing number of organisms from inanimate sources, particularly fungi, are now being recognised as playing a part in human disease.

SPREAD OF INFECTION

The Routes of Transmission of Micro-organisms

(1) **Autogenous Sources.** The pathogenic organism may invade directly from the site at which it is growing—e.g. a commensal *Staph. pyogenes* may cause a boil or the micro-organism may spread locally to different sites on the body surfaces. Thus *Strept. pyogenes* from the nasopharynx may cause erysipelas of the face, or *Esch. coli* from the large bowel may pass from the anus to the urethra and invade the urinary tract. Alternatively the transmission may be by the blood stream, as when a tooth is extracted and *Strept. viridans* from the mouth enters the blood and colonises abnormal heart valves and produces bacterial endocarditis.

(2) **Exogenous Sources.** (*a*) DIRECT ROUTE. Spread of micro-organisms from source to host may lead to contamination of the skin, conjunctiva or mucous membrane by direct contact. This may occur in the transmission of:

- (i) Skin diseases such as impetigo, erysipelas, superficial fungal diseases and scabies.
- (ii) Venereal diseases such as syphilis, gonorrhoea, trichomoniasis, non-specific urethritis, lymphogranuloma inguinale and chancroid.
- (iii) Oral and respiratory diseases following contact such as kissing, e.g. ulcerative gingivitis and upper and lower respiratory tract infections due to bacteria and viruses. Infectious mononucleosis has been termed the 'kissing disease'.

(*b*) INDIRECT ROUTE. When the route of spread is *indirect*, *reservoirs* are involved. Reservoirs are sometimes wrongly regarded as sources of infection but differ in that there is no significant growth and multiplication of organisms in reservoirs. There are exceptions to this definition, e.g. milk and meat are reservoirs which will support the growth of some pathogens, but the distinction is generally useful. Indirect routes of spread are (i) airborne, (ii) milk, food, water, (iii) fomites, (iv) animals and insects, and (v) instruments.

(i) *Airborne Infection.* This includes transmission by airborne droplets, droplet nuclei and dust particles. During breathing and talking organisms present in the nasopharynx, throat and mouth are expelled in *droplets* of secretion; the more violent expirations of sneezing project many more droplets for distances up to 12 feet, and coughing similarly disseminates organisms from the bronchial tree. Such droplets may be inhaled directly into the respiratory passages of new hosts. It is thus important to teach persons not to spit and to cover the mouth and nose with a clean handkerchief during coughing and sneezing. Medical attendants should wear suitable masks during operations, the dressing of wounds and on other occasions when the patient is at particular risk.

When these infected droplets dry, a protective layer of protein enables the organism to survive for variable periods. These dry droplets are called *nuclei*; the smaller nuclei remain permanently airborne while the larger settle on exposed surfaces, and along with other particulate material derived from mineral sources, clothing, handkerchiefs, bedclothes, carpets and screens, and from human and animal surfaces, contribute to the *dust* and its microbial flora. These infective particles may be inhaled or contaminate body surfaces or wounds. This mode of spread is especially important in streptococcal and staphylococcal infection in hospital and in the transmission of a number of respiratory diseases.

The spread of infection is mainly airborne in diseases of the upper and lower respiratory tract, in meningococcal infection and in many of the common infectious diseases of childhood. The risk can be reduced by fresh air, sunlight and good ventilation. In hospitals and institutions there should be an adequate distance between beds to prevent direct droplet spread; dust should be reduced by damp dusting and vacuum cleaning, and contaminated sources of particles such as bedclothes should be frequently cleaned or sterilised.

(ii) *Water-, Milk- and Food-borne Infection.* Pathogens transmitted by these vehicles are usually ingested and, as distribution may be wide and often simultaneous, epidemic outbreaks frequently occur, e.g. the enteric fevers and other salmonelloses, bacillary dysentery, cholera, hepatitis and enteroviral infections such as poliomyelitis. These infections are further disseminated by the faecal-oral route with the human hand as an important vehicle.

Water supplies may be contaminated from human or animal excreta; there may be faulty disposal of sewage and seepage from cracked drains may contaminate water in wells or pipes.

Organisms such as leptospires from animals may contaminate water and invade the mucosa of man when he is immersed, e.g. in Weil's disease due to *Leptospira icterohaemorrhagiae*.

Milk and food may be contaminated by infection in the animals which provide them and thus transmit diseases such as brucellosis and salmonellosis. Possibly more common is the contamination of milk and food during collection, preparation and distribution by infective handlers, or by vermin or flies. Subsequent multiplication may take place so that large numbers of organisms are ingested by the human host. Milk- and food-borne disease can be prevented by strict public health control of the source and supply of these products. Hand washing, especially by food handlers, is a vital factor in the prevention of infection transmitted by the faecal-oral route.

(iii) *Transmission by Fomites.* Fomites is the term used to describe inanimate articles in the environment such as clothing, blankets, table ware, drinking glasses, instruments and furniture and these frequently act as reservoirs for infection. Micro-organisms may survive longer on the surface of some fomites than others and their removal is much easier from smooth hard surfaces, e.g. glass or formica, than from the interstices of fabric. Thus disinfection by physical and chemical measures is important in the prevention of spread of infection by fomites.

(iv) *Animal or Insect-borne Infection.* Many animals may aid the spread of disease in a purely mechanical way by coming into contact with sources and reservoirs of infection, e.g. flies becoming contaminated with faeces.

Blood-sucking insects may play a more specific part in the life cycle of a parasite, e.g. in plague where the rodent flea derives the causative organism from the blood of the infected animal and subsequently transmits it to other rodents and occasionally to man. The plague bacillus however goes through a growth cycle in the flea in which it also produces disease. Many widespread epidemic infections due to viruses, rickettsiae, bacteria and protozoa are spread by blood-sucking insects.

(v) *Instrument-borne Infection.* The medical and allied professions may introduce infection through imperfect sterilisation of instruments, by the transfusion of blood, plasma or serum, or by the inoculation of contaminated material. The most common of these infections is virus B (serum) hepatitis which follows at least one in a thousand blood transfusions and has a significant mortality. Introduction of organisms into the bladder by catheterisation is very common and infection may follow particularly if the instrument is indwelling. Accidental inoculation of organisms into the spinal canal carries a high chance of infection because of the poor defences of the cerebrospinal fluid. Serious infections following inoculation into other sites, such as a joint, occasionally occur.

Incubation Period

The period of time which elapses between the invasion of the tissues by pathogens and the appearance of clinical symptoms and signs of infection is called the *incubation period* of the disease. Its duration varies: in diphtheria it is about three days, in measles about 10 days, in viral hepatitis type A two to six weeks, in type B two to six months, and in leprosy one to several years. The incubation period tends to be shorter when the inoculum is large.

The Process of Infection

The micro-organism must invade the tissues before infection can result. Normally invasion is preceded by *contamination* of a body surface. Under certain conditions a pathogen will *colonise* a surface after contamination and become a commensal, e.g. *Staph. aureus*. *Invasion* will occur only if the surface defence mechanisms are breached. Following invasion, *infection* will take place only if the organism survives and multiplies at a rate faster than the tissue defence mechanisms (p. 49) can prevent these processes.

Many, if not all, of the changes which take place during the growth of pathogenic micro-organisms in the tissues can be attributed to certain products of the organism and these may be conveniently referred to as '*toxins*'. Some of these are highly specific in their effect so that a characteristic clinical syndrome may be produced, e.g. scarlet fever, diphtheria, or tetanus; others are less characteristic and their effects may appear to be similar to those produced by other infections. Thus all infections are associated to a greater or lesser extent with *toxaemia* due to toxins circulating in the blood and body fluids.

Progressive growth and increase in numbers of the pathogen leads to local and often more general destruction of tissue and this may result in the formation of pus; or the function of the greater part of an organ may be grossly upset, as in viral hepatitis. Invasion of the lymphatic system will result in *lymphangitis* and *lymphadenitis* and invasion of the blood stream in *bacteraemia*, *viraemia*, *fungaemia* or *protozoaemia*. The micro-organism may thus be disseminated throughout the body and give rise to secondary lesions; this process when productive of pus formation, is termed *pyaemia*. Continuous invasion of the blood stream and multiplication of micro-organisms therein is described as *septicaemia*.

DEFENCE OF THE HUMAN HOST

Susceptibility of Host to Infection. Many animal and human races differ in their susceptibility to infection. For example Negroes whose red cells contain haemoglobin S are relatively immune to malaria (p. 737). Man and the guinea-pig may be infected by human or bovine strains of the tubercle bacillus, but are unaffected by the avian strain. Rabbits are very susceptible to experimental infection with the bovine strain, though they seldom if ever contract tuberculosis naturally. Birds on the other hand are susceptible only to the avian variety. When measles was first introduced by traders into the Fiji Islands there was a very high mortality rate at all ages.

An unfavourable environment may decrease resistance to the infection. For instance anthrax, a serious disease in cattle and man, does not affect the normal hen, even when large doses of the organism are injected. If, however, the hen is exposed to low temperatures, inoculation of anthrax bacilli may produce a fatal disease. Similarly, if man is harbouring a pathogenic organism, exposure to cold and damp may precipitate disease.

Infants during their first six months of life are relatively insusceptible to many infections owing to transplacentally derived immunity (p. 23).

The First Lines of Defence. The surface barriers, mechanical, chemical and biological constitute the first lines of defence. The skin is a substantial barrier; the efficacy of the physically weaker mucous membranes, such as the lining of the respiratory and gastrointestinal tracts and the conjunctival sac is increased by supplementary defences which are mainly chemical. The secretions of mucous membranes are sticky and trap micro-organisms and they also contain antimicrobial substances, low concentrations of antibody (p. 24) and enzymes which inactivate and kill microbes which are not adapted to a commensal existence. The dilution of surface organisms by the flow of secretion, e.g. tears, is also of importance. Even the skin has considerable chemical defence in the antimicrobial secretions contained in sweat and sebum.

The respiratory tree, down to the level of the larger bronchioles, is lined with ciliated epithelium which collects the mucous secretions which have trapped inhaled micro-organisms and carries these upwards eventually to be swallowed. Most of the surviving organisms will be killed by gastric acid.

Practically all the body surfaces are colonised by large numbers of commensals. This flora prevents the survival of most contaminating micro-organisms, including pathogens and therefore acts as an effective defence barrier. The removal of these commensals which may occur during chemotherapy, can allow minority populations to multiply, e.g. *Candida* causing thrush; or it may allow contaminating pathogens to establish themselves and produce infection, e.g. staphylococcal enteritis.

Second Line of Defence. The first stage of infection is invasion of the tissues. Factors related to the pathogenicity of the micro-organism or accidental or surgical wounding allow penetration of the surfaces to the underlying tissues. Contamination of deeper tissues may occur directly after wounding and this bypasses the surface defences so that the deep or tissue defences are immediately called on to contain the invading micro-organisms. These defences are cellular, humoral and mechanical.

Cellular Defence. Immediately after invasion of the tissues, micro-organisms are phagocytosed by reticulo-endothelial cells, both wandering and tissue macrophages (p. 20); these deal successfully with the great majority of incidents, but if the organism is virulent and multiplies faster than the rate of phagocytosis, it will dominate. The neutrophil polymorphonuclear leucocytes, the monocytes of the blood and the cells of the reticulo-endothelial system are all phagocytic. The lymphocytes and plasma cells produce antibodies (p. 20). The role of the eosinophils which increase in number in helminthic infections, in allergic reactions and during convalescence from acute infections is unknown. Phagocytosis by leucocytes has been shown to be more efficient in the presence of specific antibody.

Humoral Defence. The role of antibodies has been described in the preceding chapter.

Mechanical Defence. In many infections a mechanical barrier forms against the spread of infection, e.g. the fibrin from the acute inflammatory reaction of a pyogenic infection, or the fibrous tissue around a tuberculous focus or a hydatid cyst. It should be remembered however that some organisms elaborate substances which weaken this defensive barrier, e.g. β-haemolytic streptococci may produce a fibrinolysin which dissolves fibrin, or hyaluronidase, a substance which enables the organisms or their products to spread more rapidly through the tissues.

REACTIONS OF THE HOST TO SPECIFIC INFECTIONS. The nature of the responses of the body and their intensity depend upon the type of infecting agent, its quantity and its virulence. Viral infections tend to excite a local lymphocytic reaction and a polymorph leucopenia with relative lymphocytosis in the blood. Rarely there is an initial polymorph leucocytosis. Worm infections are frequently associated with an eosinophilia. When the infection is bacterial, the character of the ensuing reaction varies. Pyogenic organisms (staphylococci, streptococci, pneumococci, meningococci, gonococci and *Esch. coli*) give rise to an acute local inflammation with the outpouring of neutrophil polymorphonuclear leucocytes, serum and fibrin and a general reaction of abrupt onset with pyrexia and polymorph leucocytosis. Typhoid and paratyphoid infections cause a local monocyte response, a polymorph leucopenia and a gradual increase of fever over several days. Whooping-cough induces a lymphocytosis. Tuberculosis and leprosy are more chronic infections, with a local reaction of lymphocytes and reticulo-endothelial cells; fever is less marked or may be absent and there is seldom any change in the total or differential leucocyte count.

GENERAL REACTION OF THE HOST. The course of an infection depends upon the patient's psychological, physical and nutritional state. An absence of fever and leucocytosis in pneumococcal pneumonia, for instance, indicates a poor response and a bad prognosis. This is especially liable to occur in elderly or alcoholic subjects. It has long been recognised that the mental attitude of the patient towards his affliction can affect his power of recovery. The doctor's ability to give confidence to the patient and the relatives is a very important part of treatment. Though the mechanism of this is not clear, it is known that the activity of the endocrine glands and the autonomic nervous system is to some extent controlled by psychological factors through the influence of the higher centres upon the hypothalamus. That the endocrine glands may play an important role in the defence mechanism is suggested by the increased susceptibility to and mortality from infection in diabetes mellitus and in Addison's disease, and by the powerful influence of corticosteroids for good or ill in allergic and inflammatory states.

CLINICAL FEATURES OF INFECTION

Symptoms common to most febrile infections are malaise (a feeling of ill-health), anorexia (loss of appetite), lassitude and headache. 'Hot and cold' feelings, chilliness or shivering are frequently described and are due to vasoconstriction in the skin associated with a rising temperature. Deep-seated aching in the back and limbs is common in viral infections. In addition to these general complaints, many infectious diseases cause specific or localising clinical features which may be of diagnostic value.

The rapidity of the onset of symptoms may also be characteristic. Pneumococcal pneumonia for instance has in most cases an abrupt onset with rigors (severe shivering), dry cough, pain in one side of the chest on inspiration or coughing, and the appearance of herpes on the lips. These points strongly suggest the diagnosis of pneumonia even before a physical examination has been made. Indeed in the early stages abnormal signs in the chest may not be detectable, and the diagnosis will depend upon the history and the general appearance of the patient. Typhoid fever on the other hand starts so insidiously that patients may continue with their normal occupation for a few days before seeking advice.

The following signs are common to most infections.

Pyrexia. Normal body temperature shows a diurnal variation of about 1° C., being lowest in the early morning and highest in the afternoon. The upper limits are 37·2° C. in the rectum, 37° C. in the mouth and 36·7° C. in the axilla. Pyrexia may be defined as an increase in the diurnal variation of more than 1° C. or a rise above the maximum normal temperatures just mentioned.

The rate of rise and fall of fever may be of diagnostic value. A rigor raises body temperature rapidly in spite of every indication that the patient feels cold. Heat production is increased by shivering and heat loss is decreased by constriction of the skin vessels. Rigors are common in pneumococcal pneumonia, acute pyelonephritis, septicaemia, and malaria. Subsidence of pyrexia may be rapid by 'crisis' or slow by 'lysis'. Characteristic types of fever, when they occur, are mentioned under specific conditions.

At the height of the fever the skin is hot, flushed and dry. Sweating occurs as the temperature subsides. In rheumatic fever sweating is prominent throughout. Profuse perspiration may lead to a sweat rash (sudamina) consisting of numerous minute vesicles.

Causes of fever other than infection include exercise, a hot bath, the injection of pyrogens, sensitivity to foods and drugs, severe anaemia, venous thrombosis, pulmonary, myocardial or other infarctions, connective tissue disorders, malignant growth, especially when associated with necrosis or generalised dissemination, Hodgkin's disease and pontine haemorrhage. An apparent rise in body temperature is produced not infrequently in malingerers.

Cardiovascular Signs. The heart rate is increased. There is a slight rise in the systolic and fall in the diastolic blood pressure. The result is a rapid pulse of large amplitude which is often described as bounding. For every 0·5° C. rise in temperature an increase of about 10 beats per minute in the pulse rate may be anticipated. Exceptions to this general rule are acute tuberculosis, scarlet fever and acute rheumatic carditis in which it is faster, and enteric fever, viral infections and often meningitis in which it is slower than expected from the height of the temperature.

Respiratory Signs. The respiratory rate is increased by fever in proportion to the pulse. The normal ratio of 1 : 4 is maintained except with acute infections of the respiratory tract in which this ratio is increased to 1 : 3 or 1 : 2.

Alimentary Signs. The tongue is furred and dry. Foul crusts (sordes), consisting of bacteria, food and dried saliva, may collect around the teeth and on the lips. Appetite is poor; there may be nausea, vomiting and constipation.

Urinary Signs. The urine is scanty and concentrated owing to loss of fluid by sweating. There is often a brick-red urate deposit. Proteinuria is frequently present, but it disappears on recovery from the fever without any residual renal damage.

Blood Changes. The alterations which may occur in the circulating leucocytes are indicated on page 50. In chronic infections normochromic or hypochromic anaemia may develop.

DIAGNOSIS OF INFECTIOUS DISEASE

A knowledge of infections prevailing in the locality may be an invaluable guide to diagnosis, e.g. when mumps is prevalent, the occurrence, without apparent cause, of acute epididymo-orchitis in an adult may be attributed to mumps with some confidence, a diagnosis which could not be be made on clinical evidence alone. Mild or atypical infections may be correctly diagnosed on similar grounds, e.g. infectious hepatitis without jaundice occurring in a person who has been in contact with that disease. It is wise to enquire about contacts among the family, friends and workmates. Persons following certain occupations may be unduly exposed to infection, e.g. leptospirosis (p. 82) occurs in coal miners, pig farmers, sewer-workers and fish cleaners; anthrax occurs in tanners and in handlers of imported bone meal.

A recent history of laparotomy or of obscure abdominal pain should suggest subphrenic or intrahepatic abscess.

Residence or travel abroad within the previous year or two raises the possibility of malaria, amoebic abscess of the liver or other exotic disease.

In many infections a diagnosis beyond all reasonable doubt may be made on clinical grounds, e.g. measles, chickenpox, mumps and rheumatic fever. In others there may be doubt about the identity of the causal organism and demonstration of its presence is essential for diagnosis. Other considerations such as the tracing of a carrier may make it desirable to ascertain the precise strain of organism present.

Identification of the Causal Organism

This may be made by methods of *direct diagnosis* including demonstration of the organism microscopically in preparations of tissue, exudate or excreta, isolation of the organism in laboratory culture or, more rarely, its growth in laboratory animals. In cases where these methods are inapplicable or unavailing, methods of *indirect diagnosis* must be used to demonstrate the presence of specific antibody in the patient's serum. The significance of the isolation of certain micro-organisms may require further support by the demonstration of homologous antibody, e.g. the mere isolation of an enterovirus from the faeces may be equivocal without an accompanying significant rise in corresponding antibody titre.

A number of micro-organisms are sufficiently characteristic in their morphology and in the situation from which they are obtained to enable a direct microscopic diagnosis to be made, e.g. Gram-negative diplococci of *Neisseria gonorrhoeae* in urethral exudate or of *N. meningitidis* in purulent cerebrospinal fluid; *Mycobacterium tuberculosis* in sputum stained by the Ziehl-Neelsen method; *Treponema pallidum* demonstrated in chancre fluid by dark ground illumination, or *Plasmodium* in the blood of patients with malaria. The demonstration of malarial parasites in the blood of persons living in or from countries where malaria is common does not exclude the possibility that their presenting illness is due to some other cause. It may be difficult in some of these infections to culture the organism in the laboratory so that diagnosis depends upon direct microscopy.

In the majority of infections, however, it is either not possible to demonstrate micro-organisms by microscopy because they are so sparse, or in demonstrating them in exudates it is possible to make only limited decisions as to their nature because of their uncharacteristic morphology and situation. Thus the pathogens of bacillary dysentery (*Shigella*) appear identical to the commensal *Esch. coli* so that no assistance in diagnosis can be obtained by direct microscopic examination of the stool. Similarly while Gram-positive cocci may be seen in pus, it may be difficult to do more than suggest that they are either staphylococci, streptococci, or micrococci and even this differentiation may be dubious on purely microscopic evidence. Thus in most cases it is necessary to culture a tissue fluid or exudate in order that characteristic colony growth can be obtained for fuller identification of group and species. Cultural studies are also necessary for supplementary information such as antibiotic sensitivity.

Special media, particularly tissue culture, are required for the isolation of viruses and other organisms such as rickettsia, coxiella, mycoplasma; chlamydia. A few viruses may be detected directly by electron microscopy and this is particularly useful in the differentiation of smallpox and chickenpox.

Indirect Diagnosis of Infection

The cause of infection may be inferred from the presence of specific antibody in the patient's serum. Antibodies formed in response to an infection are not present in significant amounts until about a week after the onset of the infection. The demonstration of antibodies is often of value in establishing the cause of a wide range of infections including salmonellosis, brucellosis, leptospirosis, syphilis, infectious mononucleosis and certain types of streptococcal and staphylococcal disease. The clinical value of serological tests for the individual patient is limited in most viral infections by the fact that recovery has often occurred before the result has been obtained, but these tests may be of particular value in the exclusion of mumps and smallpox.

The majority of results are reported as a titre which is the reciprocal of the highest dilution of the patient's serum producing the laboratory effect measured, including agglutination, complement fixation and haemolysis. Such figures require interpretation in the light of the clinical background of the individual patient. Frequently the antibody titre in an isolated specimen of serum is of little value since it is not referable to a previous result from the patient and the normal range of antibody values is wide. At least two specimens should be examined at an interval of not less than five days, so that a rise or fall in titre may be measured. This minimum interval may require to be longer, particularly in viral infections. In all cases the results of immunological tests must be carefully considered in relation to the patient's occupation, history and clinical findings, and also to previous artificial immunisation and residence in areas where a particular infectious disease may be endemic.

Pyrexia of Unknown Origin

(P.U.O.)

Most febrile illnesses are due to infection and often the disease can be diagnosed by clinical examination alone. In other instances a suspected diagnosis may require confirmation by haematological examination, radiography, bacteriological investigation of blood or other body fluids, discharges or excreta. Often detection of specific antibodies in the serum may have to be undertaken before the diagnostic problems can be solved. Occasionally the cause of a febrile illness remains uncertain in spite of such investigations and such a case is categorised as P.U.O. In order to establish the diagnosis the following measures should be undertaken:

1. Retake the history; a symptom may have been overlooked or misinterpreted or new complaints may have developed.

2. Repeat the physical examination of the patient; new signs may have appeared while others could have been missed or their significance not appreciated. The throat and ears of children in particular should be inspected again.
3. Examine the urine repeatedly for protein, white and red blood cells and micro-organisms.
4. Inspect the whole series of temperature charts from time to time for evidence of some characteristic appearance such as the undulations seen in some cases of reticulosis (Pel-Ebstein fever).
5. Review the results of laboratory investigations, thoroughly scrutinise any radiographs again and repeat such examinations as may seem necessary.

If the diagnosis is still uncertain, further tests will be required. These will be indicated by any new information obtained as a result of the clinical reassessment. It should be borne in mind that most problematic fevers are due to some common disorder with an unusual presentation. In the absence of clues, investigations should be planned in accordance with the most probable causes of P.U.O. taking into account age, sex of the patient and the country in which the patient has been living. In Britain the more common causes of P.U.O. can be grouped as follows:

1. *Tumours.* Hodgkin's disease and other reticuloses especially, but also carcinoma of the lung, kidney and other sites with or without metastases.
2. *Infections.* Tuberculosis (the commonest single infective cause of P.U.O.); brucellosis; infective endocarditis; biliary tract infections; hepatic, subphrenic, abdominal, pelvic or prostatic abscess; pyelonephritis.
3. *Connective Tissue Disorders.* Systemic lupus erythematosus; polyarteritis; giant cell arteritis; dermatomyositis.
4. *Hypersensitivity to a Drug.*

Investigations appropriate to these different groups include the following:

1. *Tumours.* Radiological examination of chest (P.A. and lateral) and of abdomen; pyelography; faecal occult blood tests; radiological studies of the alimentary tract; biopsy of liver, lymph nodes, bone marrow or any suspicious local lesion; laparotomy.
2. *Infections.* Cultures of the blood, marrow, urine, faeces, tissue fluids or of biopsies; serological tests; skin sensitivity tests (especially tuberculin test); abdominal radiography in the erect and recumbent position; pyelography, cholecystography, cholangiography; biopsy of liver.
3. *Connective Tissue Disorders.* Blood examination for L.E. cells; total eosinophil count; serum protein electrophoresis; rheumatoid and anti-nuclear factors in serum; biopsy of superficial arteries, skin, muscle, kidney.
4. *Hypersensitivity to a Drug.* This may happen with almost any drug but most commonly with barbiturates and penicillin or in the treatment of tuberculosis. The pyrexia subsides when the offending drug is withdrawn.

Having decided on the most hopeful line of investigation, it is a good policy to start with the simplest and least hazardous test. By reviewing the probabilities in the light of previous examinations and directing further investigations accordingly, the patient will be spared as far as possible the discomfort and dangers of unnecessary procedures.

Mysterious fevers, particularly in patients who have some knowledge of medicine or nursing, may be due to deceit (factitious fever). Doubts should be raised if the skin of a supposedly febrile patient does not feel hot or if the general health does not deteriorate in spite of persistent fever. The occurrence of some bizarre symptom or sign may arouse suspicion that the temperature is being falsified. There are both subtle and simple techniques for doing this. The latter include holding the thermometer close to a hot water bottle or other source of heat, dipping it into a hot drink, applying friction to the bulb, or shaking it in a retrograde manner.

If the diagnosis remains obscure another opinion should be obtained from an experienced physician, as reconsideration of the evidence by an unbiased observer may throw new light on the problem.

When a diagnosis still cannot be established and the patient's condition is deteriorating, various remedies, e.g. antibiotics, may be tried empirically in the hope of influencing the course of the disease. A therapeutic trial should not be regarded as a satisfactory diagnostic test and it can further obscure the diagnosis by suppressing but not curing the infection. It is most useful in suspected tuberculosis, for the combination of PAS and isoniazid (p. 366) is unlikely to influence fever of other origins.

TREATMENT OF INFECTIONS

1. GENERAL. The patient should be put to bed and protected from cold in a well-ventilated room. Daily changing of sheets and bed attire is usually necessary because of sweating, and adequate washing of the patient is essential. High fever causes discomfort which can be relieved by tepid sponging of the patient and cooling of the room. The mouth of the febrile patient is usually dry and oral toilet is necessary for comfort and to prevent thrush and suppurative parotitis. The co-operative patient is given two- to four-hourly mouthwashes with thymol glycerine compound solution or a weak solution of sodium bicarbonate (one teaspoonful to a pint of water). If the patient is seriously ill it is necessary to wipe around inside the patient's mouth. Care must be taken to prevent bed-sores by attention to pressure points, and the safe disposal of infected excreta must be arranged.

Fluid. Fluid intake sufficient to give a urinary output of at least 1,500 ml daily should be ensured. Patients left to themselves may be too ill, weak or apathetic to drink even average quantities; yet a greater fluid intake than normal is desirable since sweating increases extra-renal water loss, and the raised metabolic rate of fever requires a higher urinary output than normal to excrete the waste products of catabolism.

Food. Patients may be allowed whatever they fancy, but in a thin patient it is important to maintain a high caloric intake to prevent wasting, especially if the illness is likely to be prolonged. Anorexia is a feature of most infections and so it is usually wise to advise a light diet (Diet No. 1, p. 985).

Sleep. Insomnia should be prevented by ensuring that the bedclothes are comfortably straightened and by giving a hot drink last thing at night. When necessary hypnotics may be administered. It should be borne in mind that if cough or pain is responsible for sleeplessness, suitable symptomatic measures must be taken.

2. SYMPTOMATIC. Pain may be eased by the application of heat, by the use of analgesics such as aspirin, paracetamol, pentazocine or (occasionally) by morphine. Cough may require linctus methadone for its relief, particularly at night. Itching, sweating, constipation or diarrhoea may also require attention.

3. CHEMOTHERAPY. See pages 93 to 110.

4. USE OF SPECIFIC ANTISERA. Antisera are of value in those diseases in which an exotoxin is present, e.g. in diphtheria, tetanus, gas gangrene and botulism. With the advent of sulphonamides and the antibiotics, other antibacterial sera are no longer used at the present time.

PROGNOSIS IN INFECTIONS

Some diseases have shown a spontaneous decline in severity within living memory, e.g. scarlet fever. Infections also vary in their intensity from one epidemic to another, depending upon the resistance of the population at risk, the virulence of the parasite and the presence of secondary invaders, e.g. the 1918-19 influenza pandemic destroyed more lives in a few months than did the First World War in four years.

The prognosis of infections due to bacteria, spirochaetes and protozoa has also been entirely changed by the discovery of curative drugs. The outlook depends largely upon giving the appropriate drug in adequate dosage at the earliest possible stage of the illness.

THE PREVENTION OF INFECTION

The control of infection is largely based on three concepts:

1. *The host is separated from the parasite.* The oldest known public health measures employed isolation of the infected patient (source isolation) which remains an extremely important method of preventing the spread of infection, including that occurring in hospital. Isolation is carried to its most sophisticated development in pathogen free units (protective isolation) for the care of patients who are particularly prone to infection, e.g. those suffering from leukaemia under treatment with cytotoxic and corticosteroid drugs. The elimination of a disease from the community by finding, treating and isolating the sources of infection is an ideal which should always be vigorously pursued and it has met with considerable success in health campaigns against smallpox and tuberculosis. In highly developed countries many water- and food-borne diseases have been

largely eliminated by good sanitation and other public health measures. Individuals who have been in contact with a serious and highly infectious disease like smallpox are placed in quarantine. The term is derived from the original period of 40 days of compulsory isolation of ships after leaving a port where certain infectious diseases such as plague or cholera were raging. The duration of quarantine has come to be two days more than the maximum known incubation period of the disease in question. For the common infectious diseases of childhood, a period of observation has replaced quarantine. The probability of patients and known carriers acting as a source of infection can be reduced by isolation. Dependent upon the nature of the infection it may be necessary to disinfect or destroy surgical dressings, sputum, or excreta, to sterilise the clothing and utensils of patients and carriers, and to take special precautions against the liability of spread by those attendant upon the patient, and by those concerned with the handling of food.

2. *The micro-organism is attacked.* Most bacterial infections and many other microbial diseases are now amenable to treatment with antimicrobial agents. This has been supported by the development of effective physical and chemical means of destruction of microbes in the environment.

Autogenous infection may be reduced by good personal hygiene and by the use of topical antibacterial preparations such as chlorhexophane and chlorhexidine, incorporated in soaps, creams or sprays. Endocarditis following dental extractions in patients with valvular disease of the heart can be prevented by prophylactic antibiotic therapy. Infection arising from operations on the alimentary tract may be minimised by pre-operative suppression of the flora of the gut using appropriate chemotherapeutic agents.

In tropical diseases especially, complex biological cycles may be broken at many points and this eliminates the chance of spread. For example, malaria may be prevented by treating the whole population of an affected area, by prophylactic measures applied to all the persons at risk, by killing mosquitoes by insecticides or by attacking the larvae in their breeding grounds, and finally by eliminating the breeding grounds themselves.

3. *The resistance of the host is increased.* Apart from encouraging the maintenance of general health by adequate food, fresh air and exercise, sleep and good housing conditions, certain specific steps may be taken to increase resistance to infection. Active immunisation has been the most successful of these.

Active Immunisation. The production of antibodies may be stimulated by the injection of a suitable antigen. Some infections, such as pneumonia or influenza, do not confer lasting immunity to further attacks by similar organisms, largely because of the numerous antigenic variants involved. Other infections are followed by an almost complete and lifelong immunity and it is in members of this group that active immunisation has been found to be effective in preventing or modifying the severity of infection. The practical difficulty is to prepare antigenically effective, yet relatively non-toxic material for inoculation.

In Britain parents should be advised to have their children immunised against whooping-cough, diphtheria, tetanus, measles and anterior poliomyelitis. Expectant mothers should be immunised against poliomyelitis. Active immunisation is available for a number of other important diseases but for one reason or another is not recommended for general use within the community. Smallpox vaccination, which carries with it a small but real risk of generalised vaccinia or encephalitis, is no longer given routinely in Britain because of the very small chance of exposure to the natural disease. This is due to the success of the WHO smallpox eradication programme. However, those particularly at risk, such as hospital staff, ambulance drivers and contacts of suspected cases, should be vaccinated. Travellers to countries where the disease is still endemic or epidemic, or where a valid certificate is demanded, also require vaccination.

Because of the risk of damage to the developing embryo or fetus if rubella should occur during pregnancy, it is recommended that rubella vaccine be given to all girls between 11 and 14 years and to non-pregnant women of child-bearing age who are found to be serologically negative for this antigen. Similarly, immunisation against tuberculosis should be given to all non-reactors to tuberculin during adolescence and later in life to selected groups such as hospital and medical staff in training who may be particularly at risk.

The indications for vaccination against influenza, enteric fevers, cholera, plague, typhus, yellow fever and rabies depend upon the likelihood of exposure or international travel regulations.

At present the following schedule of immunisation is generally followed in the United Kingdom:

Age	Visits	Vaccine	Intervals
3-12 months	3	Three administrations of D.T.P.+O.P.V.	4-8 weeks and 3-6 months
12-24 months	1	Measles vaccination	
First year at school	1	Booster D.T.+O.P.V.	
8-12 years	1	Booster D.T.+O.P.V.	
10-13 years	1	B.C.G. for the Tuberculin negative	
Girls: 11-13 years	1	Rubella vaccination	
15-19 years or on leaving school	1	T.T.+O.P.V.	

D.T.P. = Diphtheria, tetanus, pertussis ('triple') vaccine.
O.P.V. = Oral poliomyelitis vaccine.
D.T. = Diphtheria, tetanus vaccine.
T.T. = Tetanus toxoid.

Passive Immunisation. An injection of specific antiserum will produce immunity for about six weeks only and should be followed by active immunisation with the appropriate antigen. The most common example of the use of antiserum is in protection against tetanus, but there are others. For instance, diphtheria occurring in a school may be prevented from spreading by injecting susceptible (Schick-positive) children (p. 66) with antidiphtheritic serum. Antitetanic and antidiphtheritic sera are prepared from the horse, and their injection induces the production of antibodies against horse serum. Subsequent injections of serum are therefore not only likely to be ineffective, but are also prone to cause sensitivity reactions, hence the need for following passive with active immunisation.

INFECTIOUS DISEASES

Diseases due to infection are prevalent throughout the world. This is especially the case in tropical countries where insect-borne diseases are common and in underdeveloped areas where standards of hygiene and nutrition are low. Almost half of all deaths in developing countries occur in children under the age of 5 from a combination of infection and malnutrition. The main groups of organisms involved are metazoa, protozoa, fungi, bacteria, mycoplasmas, rickettsiae and the viruses. Infections due to metazoa and protozoa occur mainly in tropical areas; thus helminthic infections, malaria, amoebic dysentery, sleeping sickness and leishmaniasis are common diseases in tropical Africa, Central and South America and large parts of Asia but are relatively rare elsewhere. Fungi which cause ringworm of the skin and *Candida* which cause thrush infections are common all over the world but systemic infection with other fungi such as *Blastomyces*, *Histoplasma* and *Coccidioides* are greatly restricted in their geographical incidence.

The range of bacteria is large and so is the variety of diseases that they cause; streptococci and staphylococci are widespread and produce similar diseases in every part of the inhabited globe. Others such as the cholera vibrio and plague bacillus are often productive of epidemics. Some bacterial infections may be acute such as diphtheria and tetanus, others chronic such as tuberculosis, syphilis and leprosy.

Organisms smaller than true bacteria, the rickettsiae which cause typhus fevers, the mycoplasmas of atypical pneumonia and the chlamydiae (bedsoniae) of psittacosis, lymphogranuloma and trachoma are now recognised to be widespread and are susceptible to chemotherapy. Thus most bacterial, protozoal and fungal infections can be successfully treated with antibiotics and chemotherapeutic agents provided that the appropriate drug is prescribed early in the disease. This emphasises the need for rapid and accurate diagnosis supplemented where necessary by specific tests to indicate the most effective therapeutic agent. In a few instances specific antibody treatment is also used as in tetanus, diphtheria and gas gangrene.

As yet few specific therapeutic measures are available for viral diseases, among which are the exanthemata—chickenpox, smallpox, measles and rubella; mumps and glandular fever; respiratory illnesses such as the common cold, pharyngitis and influenza; diseases of the nervous system such as rabies and other forms of encephalitis, poliomyelitis and choriomeningitis, and liver disorders such as infective hepatitis and yellow fever. The problem of chemotherapy is to control the growth and propagation of the virus without damage to the host cell on which it is so dependent. The number of viral infections for which prophylaxis is available is increasing in parallel with modern advances in virology and now there is preventative treatment for smallpox, rabies, yellow fever, poliomyelitis, measles and rubella. Several viral infections may be prevented temporarily by passive immunisation with human gamma globulin. Control over viral infections is in fact comparable to the position of bacterial infection prior to the revolution in chemotherapy which began with the introduction of sulphonamides in 1935.

Infectious diseases which involve one system predominantly are described in the appropriate chapter in this book. Accounts of malaria, amoebic dysentery, rabies and helminthic infections are given in the section 'Tropical Diseases and Helminthic Infections'. The infectious diseases described here are:

Bacterial

- Streptococcal infections
- Staphylococcal infections
- Whooping-cough
- Diphtheria
- Typhoid and paratyphoid fevers
- Bacterial food poisoning
- Bacillary dysentery
- Tetanus
- Brucellosis
- Gonorrhoea
- Syphilis
- Leptospirosis

Viral

- Measles
- Rubella
- Mumps
- Chickenpox
- Smallpox

Streptococcal Infections

Haemolytic streptococcal infection results in features which vary with the invasiveness of the organism, with its capacity to produce toxins, with the site of infection and with the reaction of the host to the infection. If the resistance to infection is low and the invasive properties of the haemolytic streptococcus high a rapidly spreading erysipelas, with cellulitis, lymphangitis or bacteraemia, may result. The haemolytic streptococcus may produce a specific exotoxin causing a widespread punctate erythema. In some persons erythema does not appear because the erythrogenic toxin is neutralised by specific antibodies produced as a result of previous haemolytic streptococcal infection. When the infection is associated with such a rash the syndrome is known as scarlet fever.

Haemolytic streptococci may be classified by precipitin tests (Lancefield) into fifteen groups. The majority of strains causing significant infection in man belong to group A (*Strept. pyogenes*). These may be further subdivided by agglutination tests (Griffith) into over 40 types. The same type of streptococcus may produce in one person acute tonsillitis, in another scarlet fever and in a third erysipelas. Prior to the discovery of the sulphonamides, streptococcal infection frequently caused very serious disease. Apart from the development of effective chemotherapeutic control, however, streptococcal infections have been undergoing a spontaneous decline in their severity.

Scarlet Fever

Although scarlet fever is at present a mild disease, it may not necessarily remain so, as fluctuations in its severity have been recorded for the past two or three hundred years. The primary site of infection in scarlet fever is usually the pharynx or the tonsils but the disease may follow haemolytic streptococcal infection in other situations, e.g. in the genital tract after childbirth resulting in 'puerperal' scarlet fever or in wounds resulting in 'surgical' scarlet fever. It is transmitted by airborne infection, or more rarely by milk or ice-cream contaminated by streptococci. The disease is notifiable. The incubation period is about two to four days. Quarantine is not necessary.

Clinical Features. Scarlet fever occurs most commonly in children from 3 to 10 years of age. It has a sudden onset and the more severe cases present with a sore throat, shivering, pyrexia, headache, and vomiting. There is inflammation of the fauces; the tonsils are enlarged and may be covered with a follicular exudate which occasionally becomes confluent. The exudate may be distinguished from the membrane seen in diphtheria by its yellow appearance and the ease with which it is wiped off. There is tender enlargement of the tonsillar lymph nodes. The rash, which usually appears first behind the ears on the second day, rapidly becomes a generalised punctate erythema. It is most intense in the flexures of the arms and legs. The face is not affected by the rash, though it is usually flushed due to fever, and the region round the mouth is pale. The tongue is initially furred but shows prominent red papillae, an appearance known as the 'white strawberry' tongue. In two or three days the fur peels leaving the 'red strawberry' tongue. The rash fades in about one week and is succeeded by desquamation of the skin.

Complications. The complications are less common than formerly as a result of the mild form of the disease and the introduction of effective chemotherapy. Extension of infection along the Eustachian tubes may lead to acute suppurative otitis media. Suppurative cervical adenitis and sinusitis also occur. Rheumatic fever and acute nephritis are rare sequelae which develop two or three weeks after the onset of the illness and are due to hypersensitivity.

Diagnosis. *Infectious mononucleosis* (p. 745), *measles* (p. 84), and *rubella* (p. 86) may sometimes be mistaken for scarlet fever. Rashes resulting from *sensitivity to a drug* are more commonly encountered in adults than in children and may differ from scarlet fever in their persistence and distribution. In scarlet fever a profuse growth of haemolytic streptococci can usually be obtained from a throat swab. A high antistreptolysin O titre (ASO) can be demonstrated in the serum. Staphylococcal septicaemia can occasionally be associated with a scarletiniform skin rash.

Treatment. The treatment of scarlet fever is the same as for streptococcal sore throat. Most cases respond rapidly to phenoxymethylpenicillin in doses of 250 mg six-hourly for seven days.

Prophylaxis. An institutional epidemic calls for chemoprophylaxis with penicillin. Erythromycin is indicated for persons sensitive to penicillin.

Erysipelas

Erysipelas is an acute local haemolytic streptococcal infection of the skin. It occurs in both sexes and is much commoner in the elderly than in the young. The disease is notifiable. A quarantine period is not necessary.

Clinical Features. The onset is abrupt with local heat and pain in the infected region of the skin together with a general systemic upset. There is a rapidly spreading red patch of inflamed skin with much underlying oedema of the subcutaneous tissues. The edge of the patch is palpably raised and clearly defined and the lymph nodes draining the area become enlarged and tender. As the oedema subsides vesicles and bullae appear in the central part of the affected area. The face is involved in at least 80 per cent of all cases of erysipelas as a result of the spread of streptococcal infection from the nose or throat.

Treatment. Erysipelas is usually brought under complete control within 48 hours of treatment with penicillin; hence the prognosis is now excellent for a disease which used to be very serious.

Staphylococcal Infections

Staph. pyogenes (coagulase-positive staphylococcus—*syn. Staph. aureus*) is responsible for a wide variety of suppurative conditions such as infected lacerations, styes, boils, carbuncles, abscesses, osteomyelitis, pneumonia, necrotising enterocolitis and bacteraemia with pyaemic abscesses. Infection is derived from human or sometimes animal sources and the organisms can be grown from the nasopharynx and skin of up to 30 per cent of healthy persons. The staphylococcus is readily spread from these sites and from clothing to contaminate the dust in which it survives in the dry state for weeks or months. In hospital this organism is an important cause of wound infection, pneumonia and neonatal sepsis. Under suitable conditions it multiplies freely in food and milk and so is an important cause of food poisoning. However many infections, particularly boils, carbuncles and abscesses, are due to autogenous infection.

Strains of *Staph. pyogenes* resistant to antibiotics have increased in number since these drugs were introduced. Such strains are more commonly acquired in hospital and may give rise to small epidemics of infection. Elsewhere the majority of strains are sensitive to antistaphylococcal antibiotics although the production of penicillinase by many precludes treatment with benzylpenicillin. Necrotising enterocolitis is usually the result of the unrestricted growth of drug-resistant staphylococci in the gut following the suppression of other organisms by chemotherapy. The diarrhoea, dehydration and peripheral circulatory failure may be so severe as to resemble cholera.

Boils are satisfactorily treated with an occlusive dressing or the local application of antiseptic agents. When the severity of the disease warrants antibiotic therapy, the choice depends on whether the infection has been acquired inside or outside hospital. In the latter case the organism may be sensitive to penicillin. If the therapeutic response is not satisfactory within 48 hours, then sensitivity tests should be carried out. Since the majority of staphylococcal infections acquired in hospital are resistant to the commonly used antibiotics, the organism should be submitted to sensitivity tests at the outset. If the patient is seriously ill treatment should be commenced with cloxacillin (p. 97), unless the patient is known to be allergic to the penicillins when lincomycin or clindamycin (p. 101) should be given.

All possible care must be taken to prevent the spread of staphylococcal infection and infective patients should be isolated and barrier-nursed.

Whooping-cough

(PERTUSSIS)

Whooping-cough is a highly infectious disease of the respiratory tract caused by *Bordetella pertussis*. It is spread by droplet infection. Clinical diagnosis in the early and most infectious stage is virtually impossible so that epidemics are common. However, the incidence and severity of the disease have been decreasing over the last few years since the institution of more effective prophylactic measures. The disease is notifiable. The incubation period is 7 to 14 days to the catarrhal stage. A quarantine period is not necessary. Whooping-cough occurs at all ages but approximately 90 per cent of cases are children under 5 years of age.

Clinical Features. The first stage of whooping-cough consists of a highly infectious upper respiratory catarrh lasting about one week during which conjunctivitis, rhinitis and an unproductive cough are present. The distinctive paroxysmal stage follows and is characterised by severe bouts of coughing. The number of such paroxysms in 24 hours varies from an occasional attack to 40 or 50 and they are always more severe at night. Each paroxysm consists of a succession of short sharp coughs, gathering in speed and duration and ending in a deep inspiration during which the characteristic whoop may be heard. It may be absent in older children and in adults because the air passages are so much wider. During these paroxysms, the face becomes congested and cyanosed, the eyes bulge and the tongue is protruded to such an extent that ulceration of the frenum may occur from trauma by the lower teeth. The last paroxysm of a series frequently ends with the expectoration of tenacious mucus and vomiting. The physical signs in the chest are those of bronchitis. The paroxysmal stage lasts from one to several weeks and is followed by the stage of convalescence during which the cough becomes less frequent and the sputum less tenacious. After the illness there is usually a lasting immunity. Second atypical attacks are sometimes seen in adults who, although not seriously ill, may be greatly distressed by the spasmodic coughing.

Complications. The most important complications of whooping-cough are acute lobular pneumonia and segmental or lobar collapse which may be followed by bronchiectasis. Convulsions are of grave significance especially if they are frequent. Subconjunctival or periorbital haemorrhage, ulceration of the frenum of the tongue, and prolapse of the rectum, which are not infrequent, are relatively unimportant results of the stress of coughing. Maternal antibody may be detected in cord blood, yet neonates are highly susceptible and the mortality is greatest in the first year of life.

Diagnosis. The diagnosis of whooping-cough is very difficult in the catarrhal stage when the disease is most infectious. It can be confirmed in the laboratory by the isolation of *Bord. pertussis* from per-nasal swabs (taken from the posterior wall of the nasopharynx on small swabs passed along the floor of the nose) or less frequently from cough-plates containing selective medium. Examination of the blood shows a lymphocytosis which, however, may not develop until the disease is well established. The diagnosis is easy in the paroxysmal stage when the whoop has developed, but by this time the danger of transmission of infection has largely disappeared.

Treatment. Ampicillin may reduce the severity of the infection if taken during the catarrhal stage. Antibiotics are of no value if the spasmodic stage has been reached and they should not be used unless secondary infection occurs. The milder case need not be kept in bed, and is better out of doors. A cough suppressant such as linctus methadone may be helpful in controlling the severity of paroxysms. When the illness is of long duration and vomiting is frequent, skilled nursing will be required to maintain nutrition, especially in infants and young children. Feeds are usually accepted and retained if they are given immediately after the vomiting which frequently follows a paroxysm of coughing.

Prophylaxis. Active immunisation should be given in accordance with the instructions on page 59. It is important that the patient should be segregated as early as possible. Many of the deaths from whooping-cough occur in the first three months of life and hence very special care must be taken to avoid exposure of infants to the risk of contracting the disease. Contacts should be isolated on the first sign of catarrhal symptoms and per-nasal swabs taken.

Diphtheria

By 1946 diphtheria, which was formerly a common and lethal disease in Britain, became so rare as a result of prophylactic inoculation that many doctors have never seen it. Yet in many parts of the world diphtheria is still an important cause of illness. It is essential that doctors should press for prophylactic inoculation, for complacency due to the virtual disappearance of diphtheria is resulting in a falling rate of immunisation, and the disease has reappeared in small outbreaks. The immediate treatment of the disease is of such vital importance to the patient that the doctor must always bear the condition in mind when examining a patient who complains of a sore throat.

Infection with *Corynebacterium diphtheriae* occurs most commonly in the upper respiratory tract and sore throat is frequently the presenting feature. The disease is usually spread by droplet infection from cases or carriers. The organisms remain localised at the site of infection and the serious consequences result from the absorption of a soluble exotoxin which damages the heart muscle and the nervous system. The mortality is proportional to the virulence of the infecting organism, which varies greatly from strain to strain. Sometimes culture of a throat swab yields organisms which are morphologically and culturally identical with *C. diphtheriae* and yet are found to be non-toxigenic as shown by precipitin or animal inoculation tests.

Persons susceptible to diphtheria can be detected by the appearance of an inflammatory reaction in response to the intradermal injection of 0·2 ml of standard toxin. This is the *Schick test* and the result should be read after five to seven days. Those who are positive may be immunised with toxoid.

The infection may occur rarely on the conjunctiva or the genital tract, or it may complicate wounds, abrasions or diseases of the skin. For example, it was a frequent complication of sores during the Second World War in the Near and Far East.

The disease is notifiable. The average incubation period is two to four days. Quarantine is not necessary. Cases are isolated until cultures from six daily nose and throat swabs are negative.

Clinical Features. The diagnostic feature is the 'wash-leather' elevated membrane of variable extent on the tonsils with a well-defined edge and surrounded by a zone of inflammation. The membrane is firm and adherent. It can be swabbed off only with difficulty in contrast to the ease with which the purulent exudate of streptococcal tonsillitis can be removed. On occasion the membrane may be dirty-grey or even black due to admixture with blood. There may be swelling of the neck and tender enlargement of the lymph nodes. In the mildest infections, especially in the presence of a high degree of immunity, a membrane may never appear and the throat is merely slightly injected. In these circumstances, diagnosis cannot be made clinically but depends upon obtaining a positive culture from a throat swab.

The clinical severity and the prognosis vary with the site and the extent of the infection and the virulence of the organism which is usually high with strains causing epidemics. The disease begins insidiously. The temperature is seldom much raised although tachycardia is usually marked. The infection may remain mild if the membrane is confined to the anterior nares or the larynx or the tonsils. With anterior nasal infection there is also nasal discharge often tinged with blood. In laryngeal diphtheria there is a husky voice, a high-pitched cough, and a danger of respiratory obstruction which can be fatal. Tonsillar diphtheria usually causes a sore throat and it is commonly followed by palatal palsy. When the infection spreads towards the uvula, to the fauces and then to the nasopharynx, the patient is often gravely ill and apathetic. The complexion is pale, the pulse rapid and of poor volume and the blood pressure low. Death from peripheral circulatory failure may occur within the first 10 days. If there is haemorrhage from the throat and nose or into the skin, the disease is almost always fatal. Those who survive the earlier toxaemia may later develop arrhythmias or cardiac failure. Electro-cardiographic changes are common and are due to myocarditis. These are reversible and there is no permanent damage to the heart in those who survive.

Involvement of the nervous system sometimes occurs, and after tonsillar or pharyngeal diphtheria it usually commences with palatal palsy on about the tenth day of the illness. The voice assumes a nasal quality, while regurgitation of fluids through the nose and sluggishness of palatal movements may be observed. Paralysis of accommodation soon follows and may be inferred from the patient's complaint of difficulty in reading small print. Such paralysis may occur irrespective of the site of infection. In myopes it may pass unnoticed.

A week or two later, though somewhat rarely, the symptoms and signs of polyneuritis may develop. Recovery from such neuritis is always ultimately complete. In exceptional cases paralysis of the diaphragm and respiratory muscles may necessitate the use of a mechanical respirator.

Complications. In addition to the cardiac and neurological complications, mention must be made of diphtheritic involvement of the larynx which may result in stridor or in respiratory obstruction. The latter is more frequent at an age when the air passages are small, and immediate tracheostomy may be necessary. Occasionally acute lobular pneumonia or pulmonary collapse may result from the inhalation of membrane which has become detached.

Diagnosis. As diphtheria is now a very rare disease in Britain, routine examination of throat swabs for *C. diphtheriae* is rarely carried out. Most microbiologists expect to be specifically asked to confirm whether or not *C. diphtheriae* is present and the clinician should make this clear in his request. It must be emphasised that the diagnosis of diphtheria is primarily clinical, and laboratory confirmation may require several days. The differential diagnosis includes:

(1) *Streptococcal tonsillitis*, in which the onset is abrupt with high fever and the initial constitutional disturbance often severe. There is widespread inflammation of the throat, whereas the exudate, usually follicular but occasionally confluent, is always limited to the tonsils. It is yellowish-white in colour and is easily wiped off with a swab. *Strept. pyogenes* may be isolated on culture.

(2) *Infectious mononucleosis* which is frequently associated with an inflamed throat accompanied by exudate. There is often a petechial rash on the palate. The lymph nodes in many situations may enlarge, and the spleen may become palpable. Sooner or later the characteristic atypical leucocytes appear. A positive Monospot test confirms the diagnosis.

(3) *Vincent's infection*, in which a foul smelling ulceromembranous lesion, often spreading from the gums, is present. Constitutional disturbance is absent or slight, and the presence of spirochaetes and fusiform bacilli may be demonstrated in a stained smear.

(4) *Agranulocytosis*, *pancytopenia* or *acute leukaemia*, in any of which ulceration may occur in the throat, can be diagnosed by the characteristic blood changes (pp. 734, 744, 748).

(5) *Thrush*, due to infection by the fungus, *Candida albicans*, gives rise to white deposits adherent to the buccal mucosa, palate and tonsils. There is little inflammation surrounding the lesions. When the disease is extensive and some of the patches are confluent, it may be distinguished from diphtheria by the white colour, by the presence of multiple outlying patches which resemble milk curds, and by the absence of cervical lymphadenitis or constitutional disturbance. Microscopic examination shows the presence of budding yeast-like growths and mycelial threads.

Treatment. Upon making a clinical diagnosis of diphtheria, the case should be notified to the community medical authorities and sent urgently to a hospital for infectious diseases. If immediate hospital admission is impracticable or delayed, refined antitoxic serum (p. 24) is injected intramuscularly without awaiting the bacteriological report on a throat swab. Every moment of delay increases the danger to the patient, because toxin, once fixed to the tissues, can no longer be neutralised by antitoxin. However, horse serum, in which antitoxin is contained, being a foreign protein, is liable to cause undesirable reactions. Firstly, there may be an immediate anaphylactic reaction with dyspnoea, pallor and collapse or even death. Secondly, after 7 to 12 days so-called serum sickness, with fever, urticaria and joint pains may occur, as a rule in the absence of any previous history of inoculation of horse serum. If there is such a history, the symptoms commonly appear earlier, i.e. in three or four days. As anaphylaxis is potentially lethal, every patient must be asked whether they have ever had antiserum before and whether they suffer from any allergic disorder. In either case a small test injection of serum should be given half an hour before the full dose.

When a reaction does occur after the test dose in an allergic subject, rapid desensitisation must be undertaken with extreme caution. In all cases an ampoule of $\frac{1}{1000}$ adrenaline solution must be close at hand to deal with any immediate type of reaction.

In a very severe case the risk of anaphylactic shock is outweighed by the mortal danger of diphtheritic toxaemia and up to 100,000 units of antitoxin should be injected intravenously if the test dose has given rise to no symptoms. For cases of moderate severity 16,000-32,000 units i.m. will suffice, and for mild cases 4,000-8,000 units. After giving serum, active immunisation against tetanus should be undertaken to avoid future use of horse serum (p. 59).

Phenoxymethylpenicillin should be administered for one week to eliminate *C. diphtheriae*. Patients allergic to penicillin can be given erythromycin.

Complete rest is essential for at least three weeks owing to the danger of cardiac and circulatory failure. This period must be lengthened if there is evidence of myocardial involvement. After a moderate attack, judged by the clinical state, the patients may be fit for discharge in six or seven weeks. After severe attacks, patients may not be fit for three months, while those who develop polyneuritis may take six to nine months to recover.

Prophylaxis. The mortality rate in diphtheria, combined with the fact that the risks and cost of treatment are considerable, emphasise the necessity for active immunisation. This should be given in accordance with the instructions on page 59.

If a case of diphtheria occurs in a closed community, such as a school, a daily examination of the throat of all contacts should be made during the incubation period and swabs taken for the detection of carriers and potential cases. Those with positive throat swabs or with the slightest suspicion of clinical diphtheria should be isolated and given penicillin. All contacts should also be advised to have active immunisation or a booster dose of toxoid, depending on the history of previous inoculations.

Cases, convalescents and healthy carriers are isolated until six daily throat swabs are negative on culture.

Typhoid and Paratyphoid Fevers

(THE ENTERIC FEVERS)

In many countries where sanitation is primitive, enteric fevers, which are transmitted by the faecal-oral route, are an important cause of illness. Elsewhere they are relatively rare. Nevertheless, outbreaks occur from time to time and the infection may be contracted by persons travelling abroad.

Aetiology. The enteric fevers are caused by infection with *Salmonella typhi* and *paratyphi* which are specific human pathogens. Other members of the Salmonella group, many of which cause infection and disease in animals, produce disease in man ranging from mild food poisoning to more serious infection which may simulate many of the features of paratyphoid fever including bacteraemia. Typhoid and paratyphoid infections have a world-wide distribution and occur endemically wherever sanitation is poor and the water supply is liable to be contaminated by human excreta. In such regions flies may also transmit the disease. In Britain spread is usually by carriers, often food handlers, through the contamination of food, milk or water; infected shell fish are occasionally responsible for an outbreak. The bacilli may live in the gallbladder for months or years after clinical recovery and pass intermittently in the stools. *S. typhi* and *S. paratyphi B* are the organisms encountered in Britain.

Pathogenesis. In the initial stage the bacilli are present in the blood stream, which explains the non-specific symptoms at the outset and the great variety of complications. After a few days the organisms become localised mainly in the lymphoid tissue of the small intestine. The typical lesion is in the Peyer's patches and follicles. These swell at first, then ulcerate and ultimately heal, but during this sequence they may perforate or bleed. The mesenteric lymph nodes and spleen are enlarged.

The incubation period of typhoid fever is usually about 10 to 14 days; that of paratyphoid is somewhat shorter. The diseases are notifiable. Quarantine is not necessary, but contacts are kept under surveillance for three weeks.

Clinical Features. *Typhoid Fever.* The onset of typhoid fever is insidious and often the patient may walk about for three or four days before being forced to take to bed. The temperature rises in a step-ladder fashion over the first four or five days, being higher at night than in the morning. During this time there is a vague feeling of malaise, with increasing headache, drowsiness and aching in the limbs. There may be some cough and epistaxis is not uncommon; constipation is usually present although in children diarrhoea and vomiting may be prominent early in the illness. The pulse is often slower than would be expected from the height of the temperature. A leucopenia is a frequent finding. At the end of the first week the typical rash may appear on the upper abdomen and on the back as sparse slightly raised, rose-red spots which fade on pressure. After two or three days they disappear, to be succeeded sometimes by fresh crops of spots. About the seventh to tenth day of illness the spleen becomes palpable. It is soft and seldom extends more than one or two finger breadths below the costal margin. Often about this time constipation is succeeded by looseness of the stools (pea-soup stools), and generalised abdominal distension with tenderness in the right iliac fossa is noted. Bronchitis may develop and there may be some delirium. By the end of the second week the patient may be profoundly ill unless the disease is modified by antibiotic treatment. In the third week the patient becomes increasingly ill from toxaemia and may pass into coma and die. The prognosis may also suddenly become more grave at this stage due to haemorrhage from or perforation of the ulcerated Peyer's patches. In those who recover the temperature falls by lysis, the appetite returns, distension disappears, and strength improves. After an initial recovery a recrudescence of the disease may occur.

Paratyphoid Fever. The most common variety in Britain is due to *S. paratyphi B*. The course tends to be shorter and milder than that of typhoid fever but the onset is often more abrupt with acute enteritis. The rash may be more abundant and the intestinal complications less frequent.

Complications of the Enteric Fevers. The dangerous complications of typhoid and paratyphoid fevers are those of haemorrhage and perforation which occur at the end of the second week or during the third week of the illness. The bleeding may be sudden and very severe. The features of shock suggesting that a haemorrhage has occurred are described on page 465. Perforation usually occurs from ulcers near the ileo-caecal valve. Apart from these two main complications, almost any viscus or system can become involved as a result of the septicaemia which is present during the first week of the illness. Pneumonia, thrombophlebitis, myocarditis, myositis, arthritis, periostitis, osteomyelitis, meningitis and cholecystitis are all recognised complications.

Diagnosis. In the first week of the disease the diagnosis may be very difficult as in this invasive stage with bacteraemia the symptoms are those of a generalised infection without localising features. In a suspected case, blood should always be taken for culture. This is by far the most important diagnostic method, particularly during the first week of the disease. During this period the organism may or may not be grown from the stool and urine using selective media. The faeces will contain the organism more frequently during the second and third weeks. A white blood count may be helpful as there is typically a leucopenia.

By the second week there are usually sufficient antibodies in the serum to provide a significant agglutination titre (Widal reaction). Agglutinating antibodies to the 'H' and 'O' antigens of the causative organisms form after the second week of the disease but their detection is rarely of diagnostic value as many patients have such responses owing to previous vaccination against enteric fever. Higher titres, greater than 240, or significantly rising titres in unvaccinated persons can be more helpful in countries where the disease is rare, but where it is common, antibodies will be present from previous clinical or sub-clinical infection and obscure diagnosis. Antibodies to the 'Vi' antigens of *S. typhi* and *S. paratyphi* may be measured and are sometimes of use in detecting carriers of these organisms.

Treatment. The patient should be treated in bed at complete rest and preferably in isolation. A high standard of nursing is required with special attention to the maintenance of nutrition and fluid intake, to the care of the mouth and to the prevention of pressure sores. Scrupulous precautions must be taken against the spread of infection by the provision of special gowns and adequate washing facilities by the bedside, and sterilisation of excreta and of all articles which come into contact with the patient.

Chloramphenicol is the most commonly used antibiotic for the treatment of typhoid fever and should be given for 14 days initially in a dose of 3 g daily, reducing to 2 g daily as the patient responds. Co-trimoxazole (p. 95) is an alternative to chloramphenicol in typhoid fever and is the drug of choice for paratyphoid fever. Even with effective chemotherapy there is still a danger of complications, of recrudescence of the disease and of the development of a carrier state. For at least three weeks the patient must be kept under careful supervision while healing of the bowel takes place. For the first few days a semifluid diet should be given, followed by the low roughage diet (Diet 1, page 985). A second course of chemotherapy must be given in the event of a relapse and this usually produces good results. The chronic carrier should be treated for several weeks with co-trimoxazole, as chloramphenicol has proved ineffective in these circumstances and its prolonged use is undesirable. In some cases cholecystectomy may be necessary.

The treatment of haemorrhage is described on page 466. Prior to the introduction of chloramphenicol the treatment of perforation was by immediate recourse to surgery, which carried a high mortality in the seriously ill. Such patients can be treated conservatively while chloramphenicol is continued, but advice from a surgeon should be sought.

The patient should be considered as infective until six consecutive stools are found to be negative on culture.

Prophylaxis. Those who propose to travel or live in countries where enteric infections are endemic should be inoculated with vaccine containing killed *S. typhi* and *S. paratyphi* A and B (T.A.B.) and if exposure to *S. paratyphi* C is likely as in East Asia, a vaccine containing this organism should be used. Vaccination is believed to produce a degree of immunity for about two years. Normally a subcutaneous injection of 0·5 ml of T.A.B. is followed by 1·0 ml ten days later. Booster doses are required after two years.

Bacterial Food Poisoning

Food poisoning includes a number of disorders presenting with diarrhoea and vomiting due to acute gastroenteritis developing up to 48 hours after the consumption of food or drink. It is customary not to include under this term the enteric fevers (p. 69), dysenteries (p. 74) and cholera (p. 974) which are also spread by infected food and drink. In contrast to enteric fever which is relatively uncommon and cholera which has been almost unknown in Britain for the last 100 years, there is an increase in the reported incidence of food poisoning, of which that of bacterial origin is by far the most common type.

Food poisoning may also be due to intestinal allergy, e.g. to shellfish, or to children eating unripe fruit or other unsuitable foods. Rarely a poisonous substance may be eaten, e.g. *Amanita phalloides*, in mistake for a mushroom or a chemical poison in food may be unwittingly consumed. Examples of the latter range from barium carbonate used in baking in mistake for flour, to arsenic or powdered glass administered murderously in the tradition of the Borgias.

Food which has been placed in a container previously used for holding a chemical poison may be contaminated. Placing acid fruit juices in cheap enamel or zinc vessels may result in the liberation of antimony or zinc. Home-made wine kept in glazed earthenware containers may be the source of chronic lead poisoning.

Aetiology. Bacterial food poisoning is usually divided into the infection and toxin types.

INFECTION TYPE. The organisms mainly responsible belong to the Salmonella group whose source is certain birds, cattle and reptiles, such as pet tortoises. The domestic fowl is one of the commonest sources of salmonellae and modern methods of poultry husbandry involving battery-rearing and deep-freezing of carcasses encourage the spread and transmission of infection, the organisms surviving in the frozen birds. *Salmonella typhimurium* causes at least three-quarters of the cases of food poisoning of the 'infection' type in Britain. Food may be contaminated with infected excreta of mice or rats, or infection may be transferred by flies or by human carriers employed in the handling of food. The size of the infecting dose of bacteria bears a close relationship to the speed of onset of symptoms and to the severity of the illness. This indicates the dangers of bacterial multiplication which may take place when food is contaminated and thereafter remains warm for many hours or days. The types of food which are particularly likely to be affected are twice-cooked meat dishes, stews, gravies, soups, custards, milk and synthetic cream. The danger of food poisoning is greatly reduced if such foods are kept in a refrigerator. Ducks tend to be carriers of salmonella organisms in the oviduct and alimentary tract, and duck's eggs are not suitable for the preparation of lightly cooked foods. Hen's eggs are rarely affected.

TOXIN TYPE. Such poisoning is most commonly caused by the enterotoxin produced by *Staph. aureus*. This frequently originates from a food handler who may be a carrier or suffering from a septic lesion and so contaminates food. Incubation under suitable conditions of temperature leads to growth of the organism and production of toxin which is relatively heat resistant and may not be destroyed by cooking. Strains of *Clostridium welchii*, many of them relatively resistant to heat, may contaminate certain foods, particularly meat. Pre-cooking of stews and pies may not destroy all the spores and the keeping of such food, even when followed by heating before consumption, will lead to the formation of toxins which can give rise to gastroenteritis, sometimes severe. Other bacteria (e.g. Streptococcus and Bacillus) may contaminate food without obvious spoilage and may also cause mild gastroenteritis.

Outbreaks of food poisoning affecting large numbers of persons occur in canteens, restaurants, hospitals and other institutions.

Clinical Features. The simultaneous occurrence of symptoms in more than one member of a household or institution often simplifies diagnosis. The incubation period is a useful pointer to the aetiology. If vomiting starts within 30 minutes of the ingestion of suspected food, it is likely to be due to a chemical poison; if it arises 12 to 48 hours later, it is probably due to a Salmonella infection. The incubation periods of staphylococcal and clostridial food poisoning are usually intermediate between these extremes being from one to 12 hours.

The symptoms in any single outbreak vary in severity depending on the type and amount of the poisonous substance ingested. The principal symptoms are nausea, vomiting, diarrhoea and central abdominal colic. Staphylococcal food poisoning may be associated only with vomiting while diarrhoea and abdominal pain are more prominent with *Cl. welchii* toxins. In severe cases there may be prostration, collapse and signs of dehydration. In the chemical and toxin types of food poisoning the onset tends to be sudden and severe and the patient may rapidly become shocked. Recovery however usually occurs within 24 hours. In the infection type, symptoms develop more slowly and there is usually pyrexia and toxicity. The patient may be ill for several days. The stools are watery and offensive, and may contain blood and some mucus, in contrast to bacillary dysentery where there is also pus.

A rare cause of bacterial food poisoning is the ingestion of one of the most potent poisons known to man, namely the toxin produced by *Cl. botulinum*. Imperfectly treated tinned food or preserved fish may be contaminated with the organism and be the source of the toxin. The clinical features differ from all other types of bacterial food poisoning and consist chiefly of vomiting, constipation, thirst and the secretion of viscid saliva and of ocular and pharyngeal pareses and aphonia.

Diagnosis. A specimen of the patient's stool or vomit together with the suspected food, if available, should be sent for culture. Organisms of the Salmonella group can usually be readily isolated. In more severe cases blood should be sent for culture. Notification of Salmonella infection and other types of food poisoning is compulsory in Britain.

Food poisoning must be differentiated from acute surgical abdominal emergencies especially in children.

Treatment. Most cases are mild and can be treated at home. Solid food should be withheld and the patient instructed to take fluids only. A quarter teaspoonful of table salt added to one pint of water flavoured with a small quantity of fruit juice provides a satisfactory oral replacement solution. Patients who are severely ill, collapsed or dehydrated require intravenous fluid therapy.

Symptoms normally pass off spontaneously in a day or two. When acute symptoms cease, semi-fluid low-roughage diet may be taken containing bread, butter, eggs, fish, soft puddings and jellies (Diet 1, p. 985). To control diarrhoea, kaolin mixture may be given in 10 ml doses every two to four hours. Codeine phosphate 30 mg six-hourly is also useful.

Antibiotics should not be given for acute diarrhoea and vomiting as they are ineffective and frequently exacerbate symptoms. If salmonella bacteraemia is suspected or confirmed, ampicillin, 1 g every six hours should be given by intramuscular injection.

If the poisoning is thought to be due to a chemical or a poisonous food, the patient's stomach should be washed out with tepid water, using the technique described on page 952.

Prevention. In Salmonella food poisoning the carrier state persists on the average for about 14 days after infection but may be much longer, and the patient must not be allowed to handle food until he has stopped excreting the organism. A reduction in the high incidence of food poisoning can best be achieved by improving the standards of personal hygiene, especially in those handling food, and by stressing the importance of hand-washing after using the lavatory. Increasing facilities for low temperature storage of food which has to be kept for some hours or days before being consumed is of the greatest importance. It is essential to keep frozen poultry at room temperature for at least eight hours before cooking or pathogens at the centre may survive unharmed.

Dysentery

Dysentery is an acute inflammation of the large intestine characterised by diarrhoea with blood and mucus in stools. Its causes are bacillary, protozoal or helminthic infection. Amoebic dysentery is described on page 970 and reference to schistosomiasis (Bilharziasis) is made on page 976.

Bacillary Dysentery

The bacilli belong to the genus *Shigella* of which there are three main pathogenic groups, *Shiga*, *Flexner* and *Sonne*, the last two having numerous strains. In Britain over 95 per cent of cases of bacillary dysentery in recent years have been caused by *Shigella sonnei*.

Epidemiology. Bacillary dysentery in endemic form is found all over the world. It occurs in epidemic form wherever there is a crowded population with poor sanitation, and thus has been a constant accompaniment of wars and natural catastrophes. Spread may occur by contaminated food or flies but contact through unwashed hands after defaecation is by far the most important factor. Lavatory chains and door handles may be contaminated even before hand washing is possible. Hence the modern provision of plenty of handbasins.

disposable towels and hot air driers goes a long way towards the prevention of the faecal-oral spread of disease. Outbreaks are not uncommon in mental hospitals, residential schools and other closed institutions. The disease is notifiable.

Pathology. There is generalised inflammation of the large bowel which may extend to involve the lower part of the small intestine. Endoscopy shows that the mucosa is red and swollen, the submucous veins are obscured and mucopus is seen on the surface. Bleeding points appear readily at the touch of the endoscope. Ulcers may form and the adjacent lymph nodes are enlarged.

Clinical Features. There is great variation in severity. Sonne infections may be so mild as to escape detection and the patient remains ambulant with a few loose stools and perhaps a little colic. Flexner infections are usually more severe while Shiga dysentery may be fulminating and cause death within 48 hours.

In a moderately severe illness, the patient complains of diarrhoea, colicky hypogastric pain and tenesmus. The stools are usually small, and after the first few evacuations, contain blood and purulent exudate with little faecal material. There is frequently fever, with dehydration and weakness if the diarrhoea persists. On physical examination there will be tenderness over the colon more easily elicited in the left iliac fossa. In Sonne infection the patient may develop a febrile illness and diarrhoea may be mild or even absent; there is usually some headache and muscular aching.

In a very small minority of cases of dysentery the diarrhoea becomes chronic and the illness then becomes indistinguishable from chronic ulcerative colitis. Arthritis or iritis may occasionally complicate bacillary dysentery.

Diagnosis. Diagnosis depends on culture of faeces. Microscopic examination of the stool shows the presence of numerous pus cells. Bacillary dysentery must be differentiated from other causes of bloody diarrhoea especially ulcerative colitis. Amoebic and schistosomiasis infections usually have a less acute onset than bacillary dysentery.

Treatment. The patient frequently retires to bed with bacillary dysentery of any severity. Mild cases, however, who may remain ambulant, should preferably be confined to the home to prevent spread of infection. Diarrhoea may be controlled by codeine or kaolin. A fluid or semi-fluid low-roughage diet (p. 985) should be given depending on the severity of the diarrhoea but if this is severe, it will be necessary to replace the water and electrolyte loss by intravenous therapy.

Bacillary dysentery is usually a self-limiting disease and antibiotics or sulphonamides are not indicated in most cases. In severe infections, especially those caused by Shiga or Flexner strains, ampicillin 500 mg six-hourly or co-trimoxazole two tablets twice daily should be given. In Britain the majority of shigellae are now sulphonamide-resistant although in tropical countries sulphonamides are still of value in severe bacillary dysentery. When they are used, an ample intake of fluids must be ensured in order to guard against anuria due to the precipitation of crystals in the kidneys.

Prophylaxis. The prevention of faecal contamination of food and milk, the isolation of cases, and the identification of carriers, are methods which are theoretically important, but may be difficult to apply except in limited outbreaks. Hand-washing is very important.

Tetanus

This disease results from infection with *Clostridium tetani*, which exists as a commensal in the gut of man and domestic animals and is found in cultivated soils. Infection enters the body through wounds, often trivial, such as those caused by a splinter, a nail in the boot or a garden fork or following septic infection such as a dirty abrasion or a whitlow. The disease is thus most commonly found in agricultural workers and gardeners. If childbirth takes place in an unhygienic environment *tetanus neonatorum* may result from infection of the umbilical stump or the mother may develop the disease.

In circumstances unfavourable to the growth of the organism, spores are formed and these may remain dormant for years. Spores germinate and bacilli multiply only in the anaerobic conditions which occur in areas of tissue necrosis or if the oxygen tension is low as a result of the presence of other organisms, particularly aerobic ones. The bacilli remain localised but produce an exotoxin with an affinity for motor nerve endings and motor nerve cells. Involvement of the former by direct spread causes local tetanus. The anterior horn cells are affected after the exotoxin has passed into the blood stream and their involvement results in rigidity and convulsions. Symptoms first appear from two days to several weeks after injury—the shorter the incubation period, the more severe the attacks and the outcome may well be fatal with an incubation period of only a few days.

Clinical Features. Much the most important early symptom is trismus—a painless spasm of the masseter muscles which causes difficulty in opening the mouth and in masticating, hence the name, 'lockjaw'. This tonic rigidity spreads to involve in turn the muscles of the face, neck and trunk. Contraction of the frontalis and the muscles at the angles of the mouth gives rise to the 'risus sardonicus'. There is rigidity of the muscles of the neck and trunk of varying degree. The back is usually slightly arched and the board-like abdominal wall resembles that seen a few hours after the perforation of a peptic ulcer, but there is little or no tenderness. In the more severe cases sudden violent spasms lasting for a few seconds to three or four minutes occur spontaneously or may be induced by diverse stimuli such as moving the patient, knocking the bed or making a noise. These convulsions are painful, exhausting and of very serious significance, especially if they appear soon after the onset of symptoms. They gradually increase in frequency and severity for about one week and the patient may die from exhaustion, from asphyxia or from aspiration pneumonia. In less severe cases convulsions may not commence for about a week after the first sign of rigidity and in very mild infections they may never appear.

Rarely the only manifestation of the disease may be *local tetanus*—stiffness or spasm of the muscles near the infected wound—and the prognosis is good if treatment is commenced at this stage. If local tetanus follows wounds of the head and neck, the resulting irritation or paralysis of cranial nerves may resemble tuberculous meningitis or polioencephalitis and in cases of doubt the cerebrospinal fluid should be examined; in tetanus it is normal. Lumbar punctures should be avoided except in cases of real doubt.

The diagnosis is made on clinical grounds. It is rarely possible to isolate the infecting organism from the original locus of entry. Spasm of the masseters due to alveolar abscess, septic throat or other causes is painful, in contradistinction to tetanus.

Prognosis. The mortality in countries where tetanus is common is nearly 100 per cent in the newborn and around 40 per cent for others, being worse for young children and the elderly. Even with all modern aids, as described below, the mortality is still considerable.

Treatment. Treatment should be begun as soon as possible and because of the technical difficulties and the seriousness of the complications, this should be undertaken in hospital. The essentials are as follows:

1. PREVENTION OF FURTHER ABSORPTION OF TOXIN FROM THE WOUND. A single intravenous injection of immune serum containing 20,000 i.u. of antitoxin should be given immediately the diagnosis is suspected. If the patient is allergic to horse serum or has received a previous injection of ATS, anti-tetanus serum prepared from sheep or human immunoglobulin anti-tetanus can be obtained. The wound requires to be thoroughly cleaned and drained if there is evidence of necrotic tissue, foreign body or sepsis. Surgery should not be undertaken until one hour after the injection of antitoxin. Benzylpenicillin should be administered in doses of 300 mg (500,000 units) twice daily as it is effective against *Cl. tetani*.

2. CONTROL OF SPASMS

(*a*) *General Measures.* The patient should lie in a quiet darkened room on a flat comfortable bed, with the bedclothes supported by a cradle. A notice should be put outside the door requesting quietness from those who pass or enter. All necessary manipulation of the patient should be done as gently as possible and with due warning, for it is unexpected stimuli which are particularly liable to provoke spasms. Expert nursing is of supreme importance.

(*b*) *Sedatives and Antispasmodics.* In most cases spasms may be prevented by diazepam. In more serious cases curare, which paralyses the neuromuscular junctions, should be given intravenously, but only if an experienced anaesthetist is available as respiration will have to be maintained by tracheostomy and intermittent positive pressure respiration. The aim of such measures is to control spasms which are terrifying, exhausting and occasionally fatal from asphyxia.

3. GENERAL MEASURES. Sufficient food and fluids are of vital importance to enable the patient to survive an ordeal which may be prolonged and violent.

In milder cases it may be possible for the patient to swallow fluids or even to tolerate a stomach tube left *in situ*. If oral treatment is impossible, intravenous feeding should be commenced without delay. The patient will probably require help in getting rid of bronchial secretions and antibiotics should be prescribed as indicated.

Prophylaxis. Active immunisation should be given in accordance with the instructions on page 59.

Contaminated injuries must be treated by the removal of all debris and non-viable tissue. The immediate danger of tetanus can be greatly reduced by the injection of a large dose of a long-acting preparation of penicillin followed by a 10-day course of oral penicillin. If wound sepsis is present cloxacillin should be given as penicillin may be inactivated by penicillinase produced by staphylococci. When the risk of tetanus is judged to be present, further protection may be given by a subcutaneous injection of 1,500 i.u. of tetanus antitoxin, after taking the precautions described on page 68 and an intramuscular injection of toxoid which should be repeated one month and six months later. For those already protected a booster dose of toxoid should be given.

Brucellosis

(UNDULANT FEVER; MALTA FEVER; ABORTUS FEVER)

Undulant fever is caused in Britain by infection with *Brucella abortus* which is usually spread to man by the ingestion of raw milk from infected cattle. It is also an occupational hazard of veterinary surgeons, laboratory personnel, slaughter-house workers and others. In Malta, the disease is due to *Br. melitensis* and is transmitted by infected goat's milk. In the USA and the Far East *Br. suis* acquired from pigs may be the causative organism. The disease is not notifiable. The incubation period is about three weeks.

Clinical Features. The disease commences as a blood stream infection and the clinical manifestations are gradual in onset and variable. The symptoms in order of frequency are sweating, weakness, headache, anorexia, pain in limbs and back, constipation, rigors, cough, sore throat, and joint pains. The spleen is palpable in about 20 per cent of cases. The temperature characteristically shows undulations, during which febrile and afebrile periods alternate over periods of a week or so. In other cases the pyrexia may be continuous and sweating may be profuse. Untreated, the disease may last for a few days or continue for many months, and in the latter case the patient often becomes extremely depressed or irritable. Neutropenia and lymphocytosis usually occur in the more severe cases. Subacute arthritis of one or more joints may develop. The spine is often the site affected and occasionally radiological changes due to osteomyelitis of a vertebra can be demonstrated. The diagnosis of undulant fever is most readily confirmed by agglutination and complement-fixation tests. Blood culture in special media should be attempted but it is rarely positive in *Br. abortus* infections in man. Other conditions causing prolonged fever must be considered in differential diagnosis (p. 55).

Treatment. Tetracycline 500 mg six-hourly for 21 days is usually effective in the acute uncomplicated case, but for the chronic or relapsing disease the triple combination of tetracycline (1 g daily), streptomycin (1 g daily) and sulphadimidine (4 g daily) is indicated for a period of two or three weeks. Co-trimoxazole may also be effective.

Prophylaxis. Undulant fever can largely be prevented by the boiling or pasteurisation of all milk used for human consumption, as *Br. abortus* is readily destroyed by heat. Eradication of the disease in animals is the most effective measure and requires slaughter of infected cattle and, where necessary, immunisation of young female calves. Such a policy has now been introduced into Britain and has already been successful in parts of Europe.

Gonorrhoea

Venereal diseases are almost invariably contracted during coitus with an infected person. Gonorrhoea and other forms of urethritis are common in Britain, but syphilis is relatively rare. About half of the male cases of venereal disease result from homosexual contacts.

Gonorrhoea is due to infection of the mucous membrane of the genito-urinary tract with *Neisseria gonorrhoeae*. The eyes, anal canal, rectum and throat may also be infected. The incubation period is about 3 to 10 days.

Clinical Features. In the male the infection starts in the anterior part of the urethra and tends to spread to the prostate and occasionally to the bladder or the epididymes. There is dysuria, some increased frequency of micturition and a white or yellow discharge from the urethra. If untreated or inadequately treated the discharge becomes less copious or intermittent, or may be observed only on waking from sleep—a condition known as gleet.

In females the infection is mainly in the urethra, the cervix uteri and the Bartholinian glands. At the onset there is dysuria, frequency of micturition, vaginal discharge and some swelling of the vulva. The symptoms may be trivial and pass unnoticed. Extension up the genital tract leads to cervicitis and acute salpingitis. Infection of the conjunctiva of infants born of infected mothers causes a profuse purulent discharge and often damage to sight. This condition, known as *ophthalmia neonatorum*, is now rare in this country, but was formerly a frequent cause of blindness. In some parts of the world the disease is still common. Systemic spread of gonorrhoea may cause acute or chronic arthritis (p. 771) and iritis. Gonococcal septicaemia may occur and can be associated with skin lesions. These vary from discrete violaceous papules or vesicles to haemorrhagic papules and pustules, often surrounded by a zone of erythema.

Diagnosis. The clinical diagnosis is confirmed by the demonstration of intracellular Gram-negative kidney-shaped diplococci in stained films of pus from the infected areas. Culture of the exudate on the appropriate medium gives a much higher percentage of positive diagnoses than reliance on microscopic examinations alone and is essential for medico-legal purposes.

Treatment. A single injection of 1·2 g (1·2 million units) of procaine penicillin is usually sufficient to cure a recent infection in a male when the gonococcus is penicillin-sensitive, but it is also advisable to give 300 mg (500,000 units) of benzylpenicillin intramuscularly and this combined therapy should be repeated in 24 hours. In the female a third injection is given and if there are any complications, treatment is continued daily for one week. Larger dosage will be required if the gonococci are relatively resistant to penicillin. Tetracycline or kanamycin are effective alternatives for patients allergic to penicillin or infected with penicillin-resistant gonococci. Gonococcal conjunctivitis responds to penicillin solution instilled into the conjunctival sac. It should also be given intramuscularly. As many cases of gonorrhoea have superadded bacterial or coccal infections of the genito-urinary tract which do not respond to penicillin, it is necessary to treat these with sulphonamides or appropriate antibiotics. In women, infection with *Trichomonas vaginalis* is also commonly present and requires treatment with metronidazole (Flagyl) 200 mg thrice daily by mouth for seven days. It is essential to establish that cure of gonorrhoea and any accompanying infection is complete by culturing secretions from the infected area. The presence of syphilis acquired at the same time as gonorrhoea may be obscured by chemotherapy; it is obligatory that serological tests for syphilis should be carried out three months after treatment.

Non-gonococcal Urethritis

(NON-SPECIFIC URETHRITIS)

In Britain urethritis in males is more commonly due to organisms other than the gonococcus. In general it is a milder and more chronic infection usually due to *Esch. coli*, staphylococci, streptococci, *T. vaginalis* or a mixture of these. Some cases may be due to infection with mycoplasmas or chlamydiae.

Treatment is by the appropriate chemotherapy, usually tetracycline. In a considerable number of patients no organism can be detected. When accompanied by other features including conjunctivitis, arthritis, balanitis or hyperkeratosis of the palms and soles, Reiter's disease is probable (p. 771); although not all cases respond to treatment, oxytetracycline is effective in about 70 per cent of patients.

Syphilis

This is a chronic infection due to *Treponema pallidum*. It is convenient to describe untreated syphilis in three stages—primary, secondary and tertiary. It must be realised, however, that the disease is generalised and continuous from the time of infection, and that it may be almost completely latent during its long course which may last for over 30 years.

Clinical Manifestations. PRIMARY STAGE. The primary lesion (chancre) develops at the site of infection. It occurs usually on the genitals, but it may be found on the lips, in the mouth, at the anus, or on a finger. The incubation period is 10 days to 10 weeks. A small painless indurated swelling forms and usually ulcerates. The regional lymph nodes are enlarged, firm, painless, and seldom suppurate.

SECONDARY STAGE. The primary lesions tend to heal, and from about the third to sixth month evidence of generalised infection becomes apparent. The patient may have malaise, headaches, sore throat and low irregular fever.

Four cardinal signs must be remembered, though any of them may be absent.

(1) *Cutaneous Rashes.* The most common early rash is a faint macular erythema which may be perceptible only in a good light. Later the rashes are characteristically polymorphic, symmetrical, of a dull red colour, do not itch and may become scaly.

(2) *Condylomata.* In moist areas, such as in the perineum, the lesions become heaped up and are known as condylomata; they contain spirochaetes and are highly infective.

(3) *Mucous Patches.* The mucous membranes of the mouth are commonly affected by shallow ulcers with a narrow red edge and a surface covered by a thin whitish membrane. Their appearance has given rise to the descriptive term of snail track ulcers. They are highly infective.

(4) *Lymphadenopathy.* There may be generalised painless enlargement of the lymph nodes.

In over 30 per cent of cases changes occur in the cerebrospinal fluid, indicating that there has been some involvement of the central nervous system; the clinical features of meningitis may be present, accompanied sometimes by cranial nerve palsies. Rarely there may be clinical evidence of involvement of any other part of the body. After several months the secondary changes gradually disappear to be followed by a latent period lasting from 2 to 30 years.

TERTIARY STAGE. In this stage lesions appear almost anywhere, but particularly in the skin and subcutaneous tissues, bone, tongue, testes, liver, aorta (p. 304) and central nervous system (p. 860). The affected structure is infiltrated with granulation tissue containing plasma cells and lymphocytes. There is endarteritis obliterans which causes necrosis. The formation of a localised necrotic swelling, which is characteristically painless, is known as a gumma.

Congenital Syphilis. The fetus may contract syphilis from an infected mother. There is then no primary stage. The damage done may be such that the child is born dead or skin eruptions may be present at birth. The child may appear to be normal at birth but fails to thrive, and within a few months presents with rashes, and signs of syphilitic disease of bone, liver, kidneys and other organs. In yet a third group of cases the overt manifestations may be delayed until late childhood, when such findings appear as deformities of bone and teeth, iritis, keratitis, juvenile tabes or general paralysis.

Congenital syphilis is now rare, as treatment of a syphilitic woman during pregnancy will ensure the birth of a normal baby.

Diagnosis. In the primary and early secondary stages, the spirochaete may be demonstrated in serum from the chancre, condylomata or mucous patches. The serological tests for syphilis become positive from about the fourth week of the disease onwards and are invariably strongly positive by the end of the third month in untreated cases. It should be realised that non-specific antigen (p. 33) is used in the usual serological screening tests—Wassermann (WR), Kahn and Venereal Disease Research Laboratory (VDRL) tests. Hence the specificity and sensitivity of such tests is variable. False positive tests may be found temporarily in glandular fever, systemic lupus erythematosus and other generalised diseases, while negative tests may be observed in many patients with late syphilis. For conclusive results additional tests which use specific treponemal antigen, e.g. fluorescent treponemal antibody (FTA) and treponemal immobilisation tests (TPI), may be required.

Treatment. *T. pallidum*, though very sensitive to benzylpenicillin, has to be exposed to it for longer periods than most micro-organisms if a spirochaeticidal effect is to be obtained. Hence the longer-acting forms of penicillin such as procaine penicillin are used. A patient suffering from early primary (sero-negative) syphilis requires 600 mg (600,000 units) procaine penicillin daily for 10 consecutive days. For sero-positive primary cases and for secondary syphilis double this dosage should be given for 20 days. Several such courses may be required for patients with tertiary syphilis. If the patient is allergic to penicillin, tetracycline should be used.

Leptospirosis

Weil's disease, an infection associated with jaundice and caused by invasion with *Leptospira icterohaemorrhagiae*, was the first leptospiral infection to be recognised in man. It was not long before it was discovered that the rat is the natural host and that the mode of spread is by contact with rat's urine containing the organism, which can penetrate the skin or mucosae.

Subsequently over 100 serotypes of leptospires have been identified, many of which have been shown to cause disease in man. The natural hosts of most of these types are small wild rodents, but some may also occur in animals such as dogs and pigs. In Britain only two serotypes, namely *L. icterohaemorrhagiae* and *L. canicola*, have been shown to cause human disease, but other serotypes have been isolated from wild rodents. The spread of these infections is usually by contamination with infected animal urine, and fish cleaners, farm-workers, veterinarians and vagrants are those most at risk; immersion in canals or stagnant water may also result in sporadic infection and in such instances the disease may present as a lymphocytic meningitis due, probably, to the entrance of the leptospires through the conjunctivae. Infections due to leptospires other than *L. icterohaemorrhagiae* are not often associated with jaundice and diagnosis frequently involves differentiation from other causes of pyrexia of unknown origin. The first step is to establish whether or not antibody to leptospiral antigen is present and this may be rapidly carried out in most laboratories. The isolation and identification of the causative organism from body fluids such as blood or urine is more difficult and time consuming.

Pathology. In patients dying from leptospirosis, there has usually been a combination of hepatic, renal and cardiac failure. The changes in the liver are non-specific; in severe cases, there may be centrilobular and even massive necrosis. Oedema and inflammatory exudate lead to intralobular biliary stasis. In the kidneys, the glomeruli are usually spared, but the tubules are affected and contain haemoglobin and myoglobin casts. The main findings in the myocardium are focal haemorrhages, interstitial oedema and cellular infiltration. A similar picture is seen in skeletal muscle. If meningitis is present, there is thickening of the meninges due to inflammatory exudate.

Clinical Features. The average incubation period is 10 days, the range being 4 to 21 days. An unknown, but significantly high proportion of infections are subclinical or may cause a mild undiagnosed fever. In the more severe infections the first or *septicaemic phase* lasts about a week. Usually the clinical illness begins abruptly with headache, severe myalgia, pyrexia, conjunctival suffusion, anorexia and vomiting. Infrequently, there are skin rashes or petechiae and enlargement of the liver and spleen.

In the second phase, sometimes termed the *toxic* or *immune phase*, leptospiral antibodies appear in the blood. The temperature falls by lysis and is usually normal for two or three days. In the majority of patients, there is further pyrexia for a few days and transient meningism (p. 855) followed by prompt recovery. In other cases, during this phase, hepatitis, tubular necrosis, myocarditis and meningitis may occur. The cause of these serious complications is uncertain but cell damage from immune complexes is a possible explanation.

Hepatitis is indicated by epigastric pain and tenderness in the right upper quadrant of the abdomen and the appearance of jaundice, usually accompanied by dark urine. There may or may not be pallor of the stools. In severe cases, jaundice deepens, there is marked anorexia and vomiting and there is a haemorrhagic tendency. The patient may worsen and show all the features of acute massive liver necrosis (p. 549). *Renal tubular necrosis* may lead to acute renal failure (p. 607). *Myocarditis* is suggested by tachycardia, fall in blood pressure and cardiac enlargement. The development of profound hypotension, arrhythmias and cardiac failure are ominous signs. *Meningitis* causes severe headache, neck stiffness and a positive Kernig's sign (p. 856). *Haemorrhagic pneumonia* and *iritis* are infrequent complications.

By the third and fourth week of the illness, the majority of patients enter the *third or convalescent phase*. The average case has a post-infective debility which gradually improves. When there has been serious involvement of the liver, kidneys and heart, mortality is in the region of 15 to 20 per cent. Those who recover, do so completely. There is gradual clearing of jaundice, the urine output improves with regression of uraemia, the blood pressure rises, the heart returns to normal size and any signs of cardiac failure disappear. During the third phase, the case untreated with penicillin may show a temporary return of muscle pains with pyrexia (secondary fever). The reason for this is not known.

Laboratory Data. Most patients with leptospirosis show a polymorphonuclear leucocytosis. When there is liver involvement, the liver function tests indicate a mild hepatocellular jaundice with an intrahepatic obstructive element; bilirubin and urobilinogen are present in the urine. In patients with renal failure the urine contains protein, red blood cells and cellular and granular casts; in severe cases the rise in blood urea is progressive. In myocarditis there is electrocardiographic evidence of conduction disturbances and arrhythmias. Meningitis is characterised by an increase of lymphocytes in the cerebrospinal fluid with little or no rise in protein; xanthochromia may be observed in the jaundiced patient. Apart from the few patients developing severe haemorrhagic pneumonia, scattered opacities probably due to haemorrhage are seen on radiography of the chest in 10 to 20 per cent of cases.

The diagnosis is made by culturing the organism from the blood in the first week or from the urine in the second and third weeks. Alternatively, blood or urine specimens may be inoculated into a guinea-pig. From the second week onwards, specific leptospiral antibodies in rising titre may be demonstrated in the blood. The serum antibody titres may not however reach diagnostic levels in those cases treated promptly.

Treatment. Leptospires are sensitive to penicillin *in vitro*. Penicillin is effective therapy in man provided it is given early enough and in adequate doses; it shortens the average illness, reduces the incidence of severe complications and abolishes secondary fever. Doubts about the usefulness of penicillin in the past arose because treatment was being initiated too late in the infection. Benzylpenicillin must be given as early as possible in the leptospiraemic phase in a dose of 300 mg six-hourly for seven days and thereafter twice daily for a further seven days. In 80 to 90 per cent of patients receiving penicillin, there is an aggravation of symptoms and a brisk rise of temperature four to six hours after the first injection and lasting for about 18 hours. This is sufficiently consistent to give valuable indirect evidence of the correct diagnosis. Appropriate fluid replacement, parenterally if necessary, is important during the period of acute illness. In severely affected patients supportive treatment for acute massive liver necrosis, acute renal failure, arrhythmias and cardiac failure may be required.

Measles

Measles is a viral disease which spreads by droplet infection. One attack confers a high degree of immunity. Most people suffer from measles in childhood, and a mother who has had the disease confers passive immunity on her infant for the first six months of life. The infection is generalised, but the clinical evidence is mainly found in the respiratory tract, the skin, the mouth and the conjunctivae. Measles is prevalent during the first six months of the year with a peak incidence in March. The disease is notifiable in England but not in Scotland. The incubation period is about 10 days to the commencement of the catarrhal stage. A quarantine period is not necessary.

Clinical Features

Catarrhal Stage. Measles commences in much the same way as a common cold. There is an acute febrile onset, with nasal catarrh, sneezing, redness of the conjunctivae, some swelling of the eyelids and watering of the eyes. In addition a short cough, hoarseness of the voice due to laryngitis, and photophobia usually appear by the second day. During the catarrhal stage, which lasts for three or four days before the appearance of the specific rash, a diagnosis of measles may be made from the presence of Koplik's spots on the mucous membrane of the mouth. These are small white spots, often compared with grains of salt, surrounded by a narrow zone of inflammation. Though often numerous on the inside of the cheeks, they may be sparse and confined to the region around the opening of the parotid duct. The disease is highly infectious during the catarrhal stage.

Exanthematous Stage. After three or four days of the catarrhal stage, the diagnostic Koplik's spots disappear while the dark red macular or maculopapular skin rash develops. The rash is first seen at the back of the ears and at the junction of the forehead and the hair. Within a few hours there is invasion of the whole skin area, and there is usually some accentuation of fever. As the spots rapidly become more numerous they fuse to form the characteristic blotchy appearance of measles. The face is ordinarily the most densely covered area. When the rash is fully erupted in two or three days, it tends to deepen in colour and then fade into a faint brown staining. Finally there is a fine, branny desquamation of the skin. The malaise and the fever subside as the rash fades.

Complications. Convulsions occur in young children and are commonest as the rash is appearing. Secondary infection by haemolytic streptococci, pneumococci or staphylococci is sometimes responsible for the development of otitis media and acute lobular pneumonia which are particularly dangerous in the first 18 months of life. Persistent conjunctivitis may be followed by corneal ulceration which, if neglected, may result in impairment of vision. Stomatitis, gastroenteritis, appendicitis and encephalomyelitis (pp. 866 and 872) may also occur.

Diagnosis. Considerable difficulty may arise in those cases in which a prodromal rash indistinguishable from *scarlet fever* develops in the catarrhal stage. However, in measles Koplik's spots are present and the eyes have the appearance of those of a child that has recently been crying. The differential diagnosis from *rubella* is discussed on page 86. It is important to remember that *drug rashes* are common and may simulate closely the eruption of measles, rubella or scarlet fever.

Treatment. The patient should be isolated if possible and excluded from school for 14 days from the appearance of the rash. Most cases of measles, in spite of the high temperature, remain uncomplicated, and antibiotics should be prescribed only for unequivocal bacterial complications. Contacts should be examined daily for the first sign of infection.

Prophylaxis

ACTIVE IMMUNISATION. One injection of live attenuated measles virus should be given subcutaneously in children over one year old who have not had the disease. This may be followed by a mild febrile disturbance.

PASSIVE IMMUNISATION. Human immunoglobulin, given intramuscularly, is recommended for the prevention or attenuation of measles, particularly for contacts under 18 months of age and for debilitated children. The dose is 250 mg for children under one year old and 500 mg for those over this age.

Rubella

(GERMAN MEASLES)

Rubella is a viral disease which spreads by droplet infection. One attack confers a high degree of immunity. The disease tends to affect older children, adolescents and young adults and it spreads less readily than measles. It occurs mainly in the spring and summer months. The disease in children is trivial. In adults the illness may be more severe, but of short duration and of little importance except when it develops in a woman during the first three to four months of pregnancy. In such cases the child may be born with a congenital malformation such as a cardiac or mental defect, cataract or deafness. The disease is not notifiable. The incubation period is usually about 18 days. A quarantine period is not necessary.

Clinical Features. In children the constitutional symptoms are so slight that the illness is rarely suspected until the rash is seen. The spots are pink macules which appear first behind the ears and on the forehead. The rash spreads rapidly, first to the trunk and then to the limbs. A minor degree of conjunctival suffusion is common. Slightly tender enlargement of the posterior cervical lymph nodes is usual and these appear before the rash or even in its absence. Neck rigidity from these inflamed nodes may occasionally raise suspicions of meningitis. Sometimes many groups of lymph nodes are affected and the tip of the spleen may be palpable. In adolescents and adults the onset may be acute with fever and generalised aches, but even then the illness lasts for only two or three days. Nearly always rubella is such a mild disease that it barely merits description were it not for the differential diagnosis, the dangers to the fetus and the occasional complication.

Complications. Polyarthritis, affecting especially the smaller joints, is undoubtedly the commonest complication and it is seen mostly in adult women. Encephalomyelitis and thrombocytopenic purpura are very rare. Complete recovery from all of them is the rule.

Diagnosis. The disease may be distinguished from *measles* by its trivial nature, its brief duration, the pink colour of the rash, the absence of Koplik's spots and the presence of enlargement of cervical lymph nodes. The morphology of the rash of rubella may vary from one epidemic to another. Sometimes, there is a close resemblance to the punctate erythema of *scarlet fever*, but in rubella the circumoral region is not spared. *Infectious mononucleosis* is another disease which should be considered in the differential diagnosis (p. 745). *Rashes due to drugs* may have a similar appearance and since they commonly occur, enquiry should always be made in regard to the taking of medicines.

The diagnosis can be confirmed by isolation of the virus or by demonstration of specific antibodies.

Treatment. No treatment is available. Indeed none is required except for non-immune women who are exposed to infection during the first three to four months of pregnancy. Then human immunoglobulin should be given at once, though its efficacy in protecting the fetus is in doubt. It is advisable to vaccinate all girls between their 11th and 13th birthdays who have not had the disease. Women of child-bearing age who are found to be serologically negative should also be offered vaccine provided that they are not pregnant and are willing to avoid pregnancy for eight weeks after vaccination.

If infection is known to have occurred during the first trimester, there is such a high chance of fetal abnormality that termination should be recommended; the chances of such abnormality following rubella later in pregnancy, although less, may also be an indication for abortion.

Mumps

Mumps is caused by a virus which spreads by droplet infection and affects mainly children of school age and young adults. The infectivity rate is not high and there is serological evidence that 30-40 per cent of infections are clinically inapparent. Most cases occur in the spring. The incubation period is about 18 days. A quarantine period is not necessary: contacts should be watched for the first sign of disease from the 12th to the 28th day after exposure.

Clinical Features. Malaise, fever and some pain near the angle of the jaw is soon followed by tender swelling of one or both parotid glands. Indeed, parotid swelling alone is often the first feature. The submandibular salivary glands may also be involved. The swollen glands subside in a few days, and may be succeeded by swelling of a previously unaffected gland. Orchitis occurs in about one in four males who develop mumps after puberty; it is usually on one side only, but if it is bilateral, sterility may be a sequel. Obscure abdominal pain may be due to pancreatitis or oöphoritis. Acute lymphocytic meningitis is another mode of presentation. Encephalomyelitis is rare. If such conditions are due to mumps, they are accompanied by a lymphocytosis. It is also of great diagnostic value in such obscure cases to know that mumps is epidemic in the district at the time.

Diagnosis. Most cases of mumps can be diagnosed on clinical grounds alone, but the diagnosis can be confirmed in doubtful cases by the demonstration of specific antibodies, or the virus may be cultured from the saliva, or from the cerebrospinal fluid in meningitis. Suppurative parotitis is distinguished by the circumstances of onset in an old, frail, ill, febrile or dehydrated patient in whom oral hygiene is poor, and confirmed by obtaining pus from the parotid duct. Calculous obstruction of the parotid duct is rare; it is relatively common in the submandibular duct where the stone can often be felt. Sarcoidosis may cause enlargement of the parotid glands and is usually painless and accompanied by other signs especially uveitis.

Treatment. Oral hygiene is important when the mouth is very dry due to lack of saliva. Difficulty in opening the mouth may necessitate feeding through a straw. Apart from the relief of symptoms as they appear, no other treatment is necessary. Orchitis can be relieved by the administration of prednisolone for a few days without apparent danger of dissemination of infection. Cases of mumps should be isolated until the gland last affected has subsided.

Chickenpox

Chickenpox is a viral infection which spreads by droplets from the upper respiratory tract or by contamination from the discharge from ruptured lesions of the skin or through contact with a patient with herpes zoster. Herpes zoster appears to be due to reactivation of a latent infection with chickenpox virus. It may be accompanied by a varicelliform rash. Chickenpox is highly infectious and chiefly affects children under 10 years of age. Most children are little incommoded by this disease but, as often happens with viral infections, adults may develop a more severe illness including a prodromal rash. A suspicion of smallpox may easily be aroused. Second attacks are very rare. In patients on long-term steroid therapy the disease may be severe or even fatal. Most recorded fatalities have been suffering from leukaemia and it is probable that the blood disorder has been the major factor in reducing resistance to the virus. The disease is not notifiable. The incubation period is about a fortnight. A quarantine period is not necessary.

Clinical Features. Constitutional symptoms are usually brief and mild, and the first sign of the disease is often the appearance of the rash. Lesions are sometimes present on the palate before the characteristic rash appears on the trunk on the second day of the illness. Then the face and finally the limbs are involved. The spots reach their maximum density upon the trunk, and are more sparse on the periphery of the limbs. The axillae should be inspected as this region is almost invariably affected, while in smallpox the reverse is true (Fig. 17). Macules appear first and within a few hours the lesions become papular and then vesicular. The vesicles are unilocular, very superficial and thin-walled. The shape is elliptical rather than spherical. Within 24 hours the lesions become pustular. The vesicles and pustules are so fragile that they may be ruptured by the chafing of garments. Damage from scratching is also frequent, since itching may be troublesome. Whether or not the pustules rupture, they dry up in a few days to form scabs. The spots appear in crops, so that lesions at all stages of development are seen in any area at the same time. The course of the disease is usually uneventful.

Complications. The only common complication is secondary infection by staphylococci and streptococci of the lesions in the mouth and on the skin. Encephalomyelitis may occur (p. 872). Chickenpox pneumonia (p. 345) or myocarditis may occur in neonatal or adult life and cause a very serious illness.

Diagnosis. Although the typical case of chickenpox presents no diagnostic problem it is important to remember that great difficulty may be encountered in cases of modified smallpox and variola minor. When the rash has fully developed, however, the peripheral distribution of the lesions in smallpox is preserved. Serious consideration of the possibility of smallpox must be given to apparent cases of chickenpox occurring in patients who have just returned from an endemic area or during an outbreak of smallpox. Typical variola major may be distinguished by certain features which contrast with those of chickenpox. In smallpox

(*a*) there is a prodromal illness of two to four days;
(*b*) the density of the lesions is greatest at the periphery, the rash is relatively profuse on convex and exposed surfaces, and the axillae are not affected (Fig. 17);
(*c*) the spots are deep-set, multilocular, circular lesions and are present predominantly at a single stage of development.

Treatment. No treatment is required in the majority of cases. Itching may be relieved by an antihistamine drug taken orally. At the first sign of secondary infection a local antiseptic should be applied to the skin, e.g. chlorhexidine (Hibitane). If bacterial infection progresses, an appropriate antibiotic should be prescribed. Children who lack natural immunity owing to leukaemia, immunological deficiency, or treatment with corticosteroid or cytotoxic drugs, and who have been in contact with chickenpox should be given an injection of anti-chickenpox gammaglobulin.

Spread of infection can be prevented by isolation of the patient and the sterilisation of all soiled articles, but the disease is usually so mild that in domiciliary practice these precautions are not normally required. The patient is no longer infectious after the skin lesions have formed scabs.

Smallpox

(VARIOLA)

The virus of variola major (severe or 'classical' smallpox) causes a highly infectious and frequently fatal disease which spreads by droplet infection from the respiratory tract or by contamination with material from the skin lesions. There are also two variants of this virus: (1) variola minor virus causes a much milder disease, which is similar in its clinical features and mode of spread, but is seldom fatal; (2) vaccinia virus (cowpox) is seldom the cause of systemic disease, and cannot be spread readily from one person to another. Immune antibodies to all these viruses are developed in response to infection by any one of them, though vaccinia gives rise to a less permanent immunity than an attack of variola. Smallpox has been eliminated from Britain, where it was at one time a terrible scourge, but it may be re-introduced from abroad: there is increased liability for this to occur since air travel has removed the time barrier of a long sea voyage. On the slightest suspicion of smallpox the community medical authorities must be notified immediately. Smallpox still constitutes a serious problem in some parts of Asia and Africa although the World Health Organisation eradication programme is slowly effecting improvements. The incubation period of smallpox is usually 12 days (extremes 7 to 16 days). The quarantine period is 18 days.

Clinical Features. In Britain there is often a history of contact or knowledge that the disease has recently been introduced into the country or that the patient has just come from abroad. In a known suspect, the disease must be considered at the onset of any febrile illness within the quarantine period, and it can be excluded only by the certain knowledge of a recent successful vaccination. Variola major begins abruptly with severe systemic disturbances which antedate the appearance of the characteristic rash. The principal symptoms of the *prodromal illness* are malaise, shivering, frontal headache, pain in the back, sore throat, cough and hoarseness of the voice. A fleeting erythematous or morbilliform rash is sometimes seen, but petechial or purpuric rashes at this stage indicate that the disease will probably be fatal. Vesicles may form on the buccal, faucial, pharyngeal, laryngeal and nasal mucosa and are soon transformed into shallow grey ulcers. On the second or third day of the illness the characteristic *skin eruption* of smallpox appears. The order of the development and the distribution of the lesions are of the utmost importance in diagnosis. Macules appear first on the forehead and the wrists, then the arms, the trunk—especially the back—then the legs. The lesions are more dense on the extremities and on the extensor surfaces than on the concavities and the flexor surfaces, and the axillae in particular are spared. The hands and forearms, the feet and legs, and the upper part of the face are covered more densely than the upper arms, the thighs and the lower part of the face (Fig. 17). The density of the

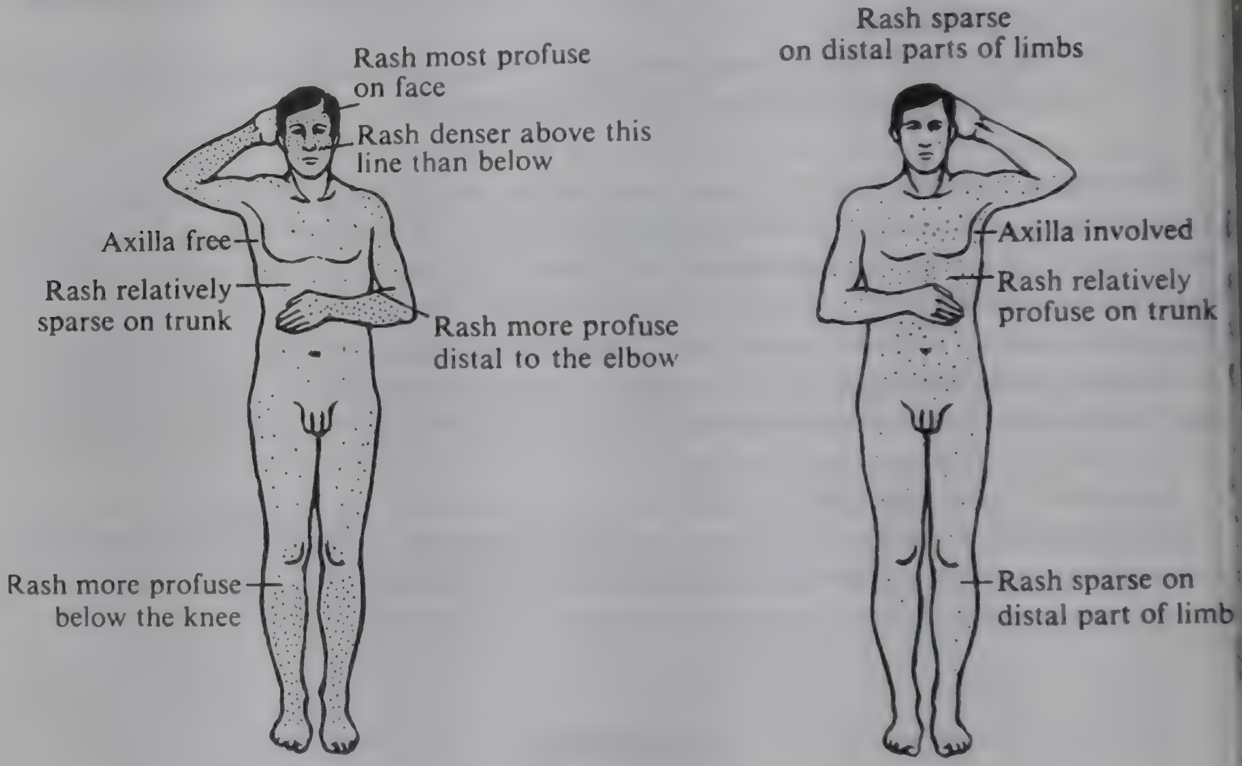

Rash most profuse on face
Rash denser above this line than below
Axilla free
Rash relatively sparse on trunk
Rash more profuse distal to the elbow
Rash more profuse below the knee
Rash sparse on distal parts of limbs
Axilla involved
Rash relatively profuse on trunk
Rash sparse on distal part of limb

FIG. 17

SMALLPOX

Note *peripheral* distribution of the rash.

CHICKENPOX

Note *central* distribution of the rash.

rash is always greater upon the limbs and forehead than upon the trunk, though the back and, to a less extent, the abdomen may be extensively affected in a severe case. It tends to be provoked by irritation and rubbing and hence the lesions are abundant over prominences and tendons. While it is usually not seen on more protected areas such as the antecubital fossae and axillae, it can be profuse in the skin folds of a fat baby's axilla. The rash develops in a regular sequence. Macules turn to deep-set, dark-pink papules in a matter of hours. The final appearance of papules may take two or three days. The conversion of papules to vesicles then commences with those lesions which were first to appear, and the whole process may take a further 24 hours. The vesicles feel hard and are not easily ruptured, for they are deep-set and multilocular. The outline of the lesions is circular. After about two days the vesicular stage merges into the pustular stage. The pustules are surrounded by a zone of erythema at first, but this gradually disappears. During the ensuing eight or nine days the pustules gradually dry up to form dark-brown or almost black scabs. These separate after several days leaving pitted scars or 'pocks'.

After the initial fever and the outbreak of the rash, the patient improves and the temperature, which falls, may even be normal for a short period. During the pustular stage, however, the temperature rises again and the patient becomes extremely toxic. The severity of this recrudescence is proportional to the extent of the rash. The patient is in a miserable state, for in addition to feeling exceedingly ill, there is oedema of the skin and ulceration of the conjunctivae, mouth, throat, larynx and trachea; a concomitant pneumonia is common.

Complications. Heart and circulatory failure may result from toxaemia. Secondary bacterial invasion of the ulcerated respiratory tract gives rise to bronchitis and acute lobular pneumonia. There may be delirium or convulsions, and encephalomyelitis may occur. Lesions of the conjunctiva may lead to corneal ulcer and impairment or loss of vision.

Differential Diagnosis. A typical case of smallpox presents little diagnostic difficulty, especially when the patient has recently come from abroad or if an epidemic is present. It is essential, however, to emphasise the fact that the diagnosis of variola minor, and particularly of variola major developing in a patient who is partially immune owing to previous vaccination (modified smallpox) may present the greatest difficulties. In variola minor or in modified smallpox the prodromal illness is less severe and the secondary fever is slight or absent. The rash may be sparse and considerably modified in many of its features, but the distribution of the lesions is nearly always typical. The trivial nature of the illness in some of these cases may result in the disease being entirely overlooked. The recognition of these infections is clearly of the utmost importance from the point of view of public health. Modified smallpox gives rise to secondary cases of variola major, whereas variola minor breeds true.

The chief differential diagnosis is from chickenpox, and the points of distinction have already been mentioned on page 89. Apparent cases of chickenpox appearing during an outbreak of smallpox, or occurring in patients who have recently arrived from regions in which smallpox is endemic should be scrutinised with the utmost care for the possibility of modified smallpox.

Laboratory Diagnosis. Most cases of smallpox have sufficient numbers of elementary particles in the skin lesions to allow of rapid presumptive diagnosis by examination of negatively stained material with the electron microscope. This method will usually distinguish variola from varicella or molluscum-contagiosum but the numbers of particles may be too small to enable them to be seen so that more sensitive cultural techniques must also be used. The virus may be isolated from the skin lesions and also from the blood in the pre-eruptive stage of smallpox by inoculation into chick embryo and a diagnosis can easily be made in this way within 72 hours. For rapid diagnosis the electron microscope examination can be supplemented by testing material from the lesion for smallpox antigen with antivaccinial serum using complement fixation and agar precipitation techniques. This method is positive in about 90 per cent of cases.

Treatment. General nursing care by attendants who have been recently vaccinated is the essence of treatment. The prevention of secondary infection by special care in the hygiene of the mouth and of the skin is of importance; when infection occurs appropriate antibacterial therapy must be employed. When the last scab has been shed the patient is no longer infectious.

Prophylaxis. Effective vaccination programmes, the isolation of cases and the quarantine of contacts have been shown to control and eventually eliminate smallpox over increasingly wider areas of the world. The reintroduction of the disease into Britain by travellers has been largely prevented by the vigilance of the health authorities; and it is now considered unnecessary to advise general prophylactic vaccination of the population.

Vaccination remains compulsory before travelling to an endemic area and under certain circumstances may be demanded by some countries for travellers coming from areas where cases are occurring. It is advised for medical staff likely to be exposed to smallpox. It is contraindicated in the presence of active skin diseases, especially infantile eczema, owing to the probable development of generalised vaccinia, which may be fatal. Should generalised vaccinia occur, the outlook can be greatly improved by the injection of human immunoglobulin. Other contraindications to smallpox vaccination include pregnancy, corticosteroid or immunosuppressive therapy and leukaemia.

Methisazone, a thiosemicarbazone, has proved to be effective in preventing the disease in close contacts and should be prescribed as early as possible in the incubation period for those in whom vaccination is contraindicated. Methisazone can be used in the treatment of eczema vaccinatum and in primary vaccination which is carried out for essential reasons in patients with the above mentioned conditions when hyperimmune γ-globulin is not available. The dose is 200 mg per kilogram followed by 400 mg per kilogram in three divided doses by mouth over 48 hours. The main side-effects of nausea and vomiting can be largely avoided by giving the drug after meals.

If a doctor suspects that a patient may be suffering from smallpox, the following procedure must be carried out:

1. The patient must not be moved from his home and if he is in hospital should be confined to a single room.

2. The community medical authorities must be notified immediately by telephone. They will arrange for a member of their panel of Smallpox Consultants to visit the patient. The consultant may:

(*a*) exclude smallpox on clinical grounds;
(*b*) confirm smallpox on clinical grounds;
or
(*c*) seek the assistance of a virologist.

3. If the disease is confirmed the patient is transferred to a smallpox hospital.

4. All immediate contacts of the patient are vaccinated and placed under surveillance at home while secondary contacts are vaccinated as indicated.

CHEMOTHERAPY OF INFECTIONS

The concept of chemotherapy is almost as old as the science of bacteriology. Attempts were made in the late nineteenth century to treat infections such as tuberculosis by the injection of other organisms or their products. The property of one micro-organism to interfere with the growth of another is called *antibiosis*, this action being frequently due to specific diffusible metabolic products of bacteria and fungi; these substances were therefore called *antibiotics*. The first to be clinically effective was tyrothricin, a product of *Bacillus brevis*, and a mixture of gramicidin and tyrocidine. Unfortunately these antibiotics are relatively toxic to leucocytes and are of value only for topical application.

In the early twentieth century Ehrlich prepared drugs by synthetic chemistry, and anti-protozoal dyes such as tryptan red and organic arsenical compounds active against spirochaetes were discovered. It was not until Domagk and Trefouel in 1935 demonstrated the therapeutic effect of sulphanilamide that successful antibacterial chemotherapy became available. Since then methodical research has produced a wide range of antibiotics starting with penicillin in 1940 and a variety of chemotherapeutic drugs such as metronidazole, co-trimoxazole, dapsone and isoniazid. A general term for all of these substances is *antimicrobial agent*. Effective chemotherapy is now available against all known bacteria, rickettsiae, mycoplasmas and chlamydia. Many specific anti-protozoal compounds are now available against diseases such as sleeping sickness, malaria and amoebic dysentery; topical antifungal agents are widely used but fully effective, non-toxic, antifungal drugs have not yet been found for use in systemic infection. In recent years antimicrobial agents active against true viruses have been discovered and a few of these have reached the stage of clinical trial and use in treatment.

In making decisions about the treatment of infections it is necessary to know the available therapeutic agents, their range of activity and their adverse effects. Consideration must also be given to factors which determine the resistance of organisms to antimicrobial agents. Finally the nature and site of the infection obviously influence the selection of therapy.

The Sulphonamides

Although the sulphonamides have been superseded in many countries by the antibiotics, their sphere of usefulness has now been extended by the introduction of co-trimoxazole, a sulphonamide combined with trimethoprim. The sulphonamides have the merit of being inexpensive but the disadvantage of having a wide range of potential dangers.

Sulphadimidine. This is the sulphonamide of choice for general purposes as it combines effectiveness with low toxicity. Sulphadimidine is rapidly absorbed and relatively slowly excreted in the urine in a fairly soluble form. An effective concentration in the blood can usually be maintained by administration every four to six hours. Sodium salts are available for intravenous and intramuscular administration if the patient is vomiting or comatose as may occur in meningococcal meningitis (p. 856). In the treatment of this condition sulphadiazine may be even more effective because it attains higher concentrations in the cerebrospinal fluid. In recent years some serotypes of the meningococcus have acquired a partial resistance to sulphonamides and in these circumstances benzylpenicillin (p. 96) should be prescribed. It is advisable to use sulphadiazine or oral penicillin as a prophylactic measure if meningococcal meningitis occurs in a closed community.

Infections of the urinary tract in domiciliary practice can often be treated successfully with sulphadimidine. A dosage of 1 g eight-hourly is adequate as the drug is concentrated in the urine. If this fails, treatment with antibacterial agents should be selected on the basis of urine culture.

Phthalylsulphathiazole. This preparation, which is poorly absorbed, is converted in the large intestine to sulphathiazole in bacteriostatic concentrations. Hence it may be given before operations on the colon since it diminishes the risk of peritonitis developing from contamination with the contents of the gut.

Sulphonamides and other antibacterial agents have been widely used in the treatment of bacillary dysentery, but such drugs are rarely indicated in Britain as the disease is often mild. Chemotherapy encourages the development of resistance to antimicrobial agents and excretion of the causative organism is often prolonged; symptomatic treatment is usually sufficient and avoids these hazards.

Long-acting Sulphonamides. The long-acting sulphonamides, such as sulphamethoxypyridazine, are rapidly absorbed and slowly excreted so that one daily dose may suffice. Apart from the convenience of less frequent administration they have no other advantages over their predecessors and, as they are more extensively bound to plasma proteins, their antibacterial action is less effective. They are also more toxic. Accordingly their use is not recommended.

Co-trimoxazole (Trimethoprim and sulphamethoxazole). The two components of this compound act by inhibiting enzymes at two successive stages in the synthesis of para-aminobenzoic acid to folic acid and DNA. Co-trimoxazole is thus bactericidal whereas sulphonamide alone is bacteriostatic. It is particularly useful in exacerbations of chronic bronchitis and infections of the urinary tract and it is also effective in the treatment of invasive salmonella infections and typhoid carriers. The adult dose is two tablets (each containing 80 mg of trimethoprim and 400 mg of sulphamethoxazole) twice daily increasing to two tablets thrice daily for severe infections. The adverse effects are those of the sulphonamides but the clinician must also be on the alert for possible haematological reactions to trimethoprim including megaloblastic anaemia and thrombocytopenia. The compound should not be given to pregnant women, the elderly, the chronic sick and others who may be folate deficient; its prolonged use should be accompanied by frequent blood counts.

ADVERSE EFFECTS OF SULPHONAMIDES

Although the sulphonamides have a wide range of potential hazards, their incidence is low when a preparation such as sulphadimidine is used. Rashes, fever, agranulocytosis, haematuria and anuria are sometimes encountered. The risks of haematuria and anuria can be decreased by ensuring an adequate output of alkaline urine. Serious but rare complications are haemolytic anaemia, purpura and pancytopenia. The Stevens-Johnson syndrome (erythema multiforme and ulceration of mucous membranes) may be induced by the long-acting sulphonamides and can be fatal. When any of the above complications develop, the drug must be stopped immediately. Cyanosis due to methaemoglobinaemia, and nausea and vomiting, which were commonly encountered with the earlier preparations, very rarely occur with sulphadimidine. Glucose-6-phosphate dehydrogenase deficiency (p. 738) is a contraindication to treatment with the sulphonamides (including co-trimoxazole) which can cause haemolysis in this condition.

Sulphonamide preparations applied to skin are liable to cause light sensitivity which may persist for a number of years; they should not be used locally. This capacity to act as a photo-sensitiser is distinct from the development of hypersensitivity to the drug itself.

The Penicillins

This group of antibiotics is composed of various penicillins, some occurring naturally and others produced by a semi-synthetic process. All are bactericidal and the range of activity of the group is now wide as both Gram-positive and certain Gram-negative organisms are sensitive to individual penicillins. The outstanding adverse effect is the risk of inducing a hypersensitivity reaction in some persons. Even so the penicillins are the most useful antibiotics at present available.

The penicillins can be subdivided into four sub-groups for descriptive purposes:

1. **Benzylpenicillin** ('Crystalline' or 'soluble' penicillin). This is the original and most active penicillin. Its action can be prolonged by combining it with

procaine—*procaine penicillin* and an even longer-acting form is *benzathine penicillin.*

2. **Phenoxymethylpenicillin and its Synthetic Analogues.** These penicillins are effective when administered by mouth as they are not destroyed by gastric acid.

3. **Cloxacillin.** This penicillin is not inactivated by staphylococcal penicillinase and is reserved for the treatment of severe staphylococcal infections resistant to benzylpenicillin. The recently introduced analogue, *flucloxacillin*, is better absorbed than cloxacillin when given by mouth.

4. **Penicillins with a Wide Range of Activity.** *Ampicillin* and its analogue *amoxycillin* are effective against Gram-negative bacilli, in contrast to the other penicillins whose activity is largely limited to Gram-positive organisms and Gram-negative cocci. *Carbenicillin* is a broad spectrum penicillin which is effective against *Ps. aeruginosa.*

1 (*a*). **Benzylpenicillin.** Benzylpenicillin is rapidly absorbed following intramuscular injection and is excreted by the kidneys within a few hours. A dose of 300 mg (half a million units) six- or eight-hourly will suffice for most infections due to sensitive organisms. Larger doses, such as 1 g, or more, intramuscularly, or in some cases intravenously produce very high blood levels of penicillin and therapeutic concentrations can be achieved within deep-seated or walled-off foci of infection, as occur in infective endocarditis or lung abscess. Large doses are painful to inject and must not therefore be administered unnecessarily. Probenecid given concurrently with benzylpenicillin will raise the blood level of penicillin by delaying its excretion by the kidney and hence reduce the size, number and pain of the injections. The dose of probenecid is 2 g daily by mouth.

Benzylpenicillin remains the antibiotic of choice for the treatment of a remarkable number of infections. These include pneumococcal, meningococcal and haemolytic streptococcal infections, endocarditis caused by *Streptococcus viridans*, gonorrhoea and syphilis, yaws, diphtheria, tetanus, gas gangrene, anthrax and actinomycosis. It is also indicated for infections caused by penicillin-sensitive strains of *Staph. aureus.*

Penicillin is also used prophylactically. Benzylpenicillin is given to all patients with valvular heart disease 30 minutes before a dental extraction to avoid the consequences of *Strept. viridans* bacteraemia. It is also given prophylactically before and after high amputations of ischaemic legs and following extensive devitalized wounds to prevent gas gangrene and tetanus.

Benzylpenicillin passes in very small quantities from the blood into the cerebrospinal fluid or through the non-inflamed pleural, pericardial or synovial membranes. In the presence of inflammation its diffusion to these sites is greater. Benzylpenicillin may occasionally have to be given by local injection when treating severe infections of the meninges, joints, pleura or pericardium.

1 (*b*). **Procaine Penicillin and Benzathine Penicillin.** These are long-acting penicillins given by injection and used in the treatment of gonorrhoea and the treponemal diseases, syphilis and yaws. *Procaine penicillin* in aqueous suspension, in a dose of 600 mg (600,000 units) intramuscularly once daily, is relatively painless and will maintain an adequate blood level of penicillin for 24 hours. *Benzathine penicillin* has a much longer duration of action than procaine

penicillin but is seldom used. A single injection of 600,000 units has proved to be an effective cure for yaws, but the blood levels are inadequate for acute infections such as pneumonia. It can be used for the prophylaxis of rheumatic fever in patients who cannot be relied upon to take oral penicillin.

2. **Phenoxymethylpenicillin and its Analogues for Oral Use.** Phenoxymethylpenicillin (penicillin V) is relatively unaffected by the acidity of the stomach and frequent oral administration will produce blood levels which in most persons are comparable with those achieved with corresponding amounts of intramuscular benzylpenicillin. The usual dose of phenoxymethylpenicillin is 250 mg every four or six hours, preferably given at least half an hour before meals to ensure maximum absorption. In seriously ill patients intramuscular benzylpenicillin is to be preferred because of uncertainties in absorption. During recovery oral therapy may be substituted in such patients.

Phenoxymethylpenicillin is indicated for minor streptococcal infections and for pneumococcal pneumonia after initial therapy with benzylpenicillin. It is used prophylactically on a long-term basis following an attack of rheumatic fever to prevent recurrences and, in the short-term, given to contacts of diphtheritic and meningococcal infections.

In addition to the obvious advantages of oral administration the severe anaphylactic reaction which occasionally follows injection is much less frequently encountered when the antibiotic is given by mouth. Provided the infection is due to an organism highly sensitive to penicillin and the patient is not unduly ill or vomiting, phenoxymethylpenicillin may be prescribed. If the patient is seriously ill, unable to swallow, vomiting or unreliable or if the organism is relatively inaccessible or only moderately sensitive, benzylpenicillin must be given by intramuscular injection.

3. **Cloxacillin.** Unlike benzylpenicillin, this semi-synthetic penicillin is unaffected by staphylococcal penicillinase. It is, however, inactivated by the penicillinase produced by other species, e.g. *Esch. coli*. Cloxacillin should be kept in reserve for the treatment of severe infection caused by staphylococci resistant to benzylpenicillin. Cloxacillin is not destroyed by gastric acidity and can be given orally. The dose is 500 mg six-hourly but for seriously ill patients treatment should be initiated by the intramuscular injection of 1 g every four hours. Cloxacillin cannot be prescribed if the patient is allergic to benzylpenicillin. In these circumstances erythromycin or lincomycin should be used.

Flucloxacillin has an identical antibacterial range to cloxacillin but is better absorbed when given by mouth.

4. **Wide Range Penicillins.** *Ampicillin* is a semi-synthetic penicillin which is effective by mouth and which has a bactericidal action against Gram-positive organisms and also a variety of Gram-negative organisms, including salmonellae, shigellae, *H. influenzae* and certain strains of *Esch. coli* and *Proteus*. It is unaffected by gastric acid but inactivated by staphylococcal penicillinase. Ampicillin is of value in urinary tract infections due to *Esch. coli* and *Proteus* and in exacerbations of chronic bronchitis. It is a less effective alternative to chloramphenicol in enteric fever but is preferable in the treatment of salmonella

carriers. The dose is 250 mg to 1 g four- to eight-hourly by mouth. Preparations for injection are also available. Maculo-papular skin rashes occur in approximately 5 per cent of all patients given ampicillin and in infectious mononucleosis they develop in over 90 per cent of patients; this antibiotic should not therefore be prescribed for sore throats which may be due to glandular fever.

Amoxycillin is a recently introduced analogue of ampicillin which has a similar antibacterial range but is better absorbed from the gastrointestinal tract.

Carbenicillin has a wider range of activity than ampicillin against Gram-negative organisms and, in particular, is active against most, but not all strains of *Ps. aeruginosa.* Unfortunately, carbenicillin can be given only by injection and its administration by the intramuscular route is painful as large quantities are necessary. The standard dose for urinary tract infections is 1 g every six hours but up to 30 g per day may be required for systemic *Ps. aeruginosa* infections, the incidence of which has increased in recent years, especially in debilitated patients and in urological wards. This antibiotic is very expensive.

Adverse Effects of the Penicillins

An increasing number of patients have acquired a hypersensitivity to the systemic administration of the penicillins. This takes the form of urticaria and pyrexia or of an acute anaphylactic reaction which has occasionally proved fatal. The factors responsible for sensitisation can be either a degradation product of the penicillin 'nucleus' or protein residues from the manufacturing process. In the former case the patient will be allergic to all the penicillins and none should be used again. In the latter case, cross-allergenicity between all penicillins does not necessarily occur. Ampicillin, for example, commonly produces a maculopapular rash which differs from penicillin-induced urticaria and is specific for ampicillin alone. It is almost certainly unrelated to true penicillin allergy and is therefore not a contraindication to future treatment with other penicillins. The patient should always be asked about previous allergy to any form of penicillin before treatment is commenced as a severe reaction may be provoked by the administration of only a few milligrams. Patients who suffer from bronchial asthma or are hypersensitive to other drugs are particularly liable to become allergic to penicillin.

Skin sensitisation may result from topical applications of any antibiotic, but such hypersensitivity to penicillin is so frequent that it should never be applied locally.

Although penicillin is otherwise a safe antibiotic, its accumulation in patients with renal failure may lead to encephalopathy, so that dosage in these circumstances must be guided by the blood levels. Benzylpenicillin is formulated as a sodium or potassium salt and hypernatraemia or hyperkalaemia can also result if large doses are given to patients with renal failure. Great care should be taken with the intrathecal administration of penicillin as fatal encephalopathy can occur if the dose (p. 108) is excessive. The routine use of intrathecal penicillin in meningitis is no longer recommended.

It is important to avoid accidental intravenous administration when injecting procaine penicillin intramuscularly as this may result in a very severe reaction consisting of a sensation of impending death, paraesthesiae and confusion lasting up to an hour and followed by exhaustion and anxiety.

Erythromycin

Erythromycin has a range of activity similar to benzylpenicillin but differs in being predominantly bacteriostatic. The main indication for its use is in the treatment of streptococcal or pneumococcal infections in patients who are allergic to penicillin. Erythromycin is prescribed in a dosage of 250 mg by mouth every six hours. Jaundice occasionally occurs with erythromycin estolate but it clears on withdrawal of the antibiotic. Allergic reactions to erythromycin are rare but diarrhoea is not uncommon.

The Cephalosporins

The cephalosporins have a structure resembling penicillin and a wide range of bactericidal activity against both Gram-positive and Gram-negative bacteria excluding *Ps. aeruginosa*.

Cephaloridine is given by injection in doses of 250-500 mg six-hourly. In very severe infections doses of up to 6 g daily can be given if renal function is normal. Cephaloridine is excreted unchanged in the urine. It is resistant to penicillinase and is well tolerated, apart from occasional renal tubular damage if large doses are given or there is pre-existing renal disease. Frusemide and cephaloridine should not be given simultaneously as there is evidence that frusemide enhances the nephrotoxicity of cephaloridine. Cephaloridine is useful in pyelonephritis, infective endocarditis and septicaemia due to Gram-negative or Gram-positive organisms.

Cephalothin is another cephalosporin which is similar to cephaloridine but less active. High doses are therefore necessary and up to 20 g per day may be required for severe infections. These doses are painful and intravenous administration is necessary. Unlike cephaloridine it is not nephrotoxic.

Cephalexin can be given by mouth in a dosage of 250-500 mg six-hourly. It is principally indicated for the treatment of urinary tract infections caused by organisms resistant to other antimicrobial agents.

Cephradine is a new form of cephalosporin which may be given orally or intramuscularly. Its range of activity and dosage is similar to that of other cephalosporins but higher blood levels are claimed.

Adverse Effects

Apart from the rare occurrence of renal damage with cephaloridine, the cephalosporins are generally very safe antibiotics. Hypersensitivity reactions occasionally occur and a very small number of people are allergic to both the cephalosporins and the penicillins.

The Tetracyclines

Chlortetracycline, oxytetracycline and **tetracycline.** These are very closely related substances which, for practical purposes, have an identical and wide range of activity. This is offset to some extent by their action being bacteriostatic and not bactericidal. The oral dose for an adult is 250-500 mg given at six-hourly intervals and taken before meals.

Chlortetracycline is used for the local treatment of skin infections as it does not cause cutaneous sensitisation.

Demethylchlortetracycline and *methacycline* attain higher and more prolonged blood levels than the other tetracyclines and hence may be given less frequently. These advantages, however, are counter-balanced by the high degree of binding to plasma proteins.

Principal Indications

The tetracyclines inhibit the growth of a wide range of Gram-positive and Gram-negative organisms and are particularly useful in the treatment of brucellosis and exacerbations of chronic bronchitis. Their value in chronic bronchitis has been limited recently by a significant increase in tetracycline-resistant pneumococci and to a lesser extent *H. influenzae*.

The tetracyclines are also active against the following organisms which are intermediate between bacteria and viruses:

(*a*) Rickettsia (typhus fevers)
(*b*) *Coxiella burneti* (Q-fever)
(*c*) *Mycoplasma pneumoniae* (atypical pneumonia)
(*d*) Chlamydiae (lymphogranuloma venereum, psittacosis).

The tetracyclines are also employed systemically in the treatment of acne vulgaris and rosacea where their beneficial effect is almost certainly not due only to their antibacterial action.

Adverse Effects

Many of the normal saprophytes of the alimentary tract are sensitive to the tetracyclines and are inhibited when these antibiotics are administered. Insensitive organisms then multiply and cause 'super-infection'. This occurs particularly with fungi, such as *Candida albicans*, which cause stomatitis, glossitis, diarrhoea or a distressing anal or vulvar pruritus. In hospital, superinfection with resistant staphylococci may occur and the ensuing enteritis, septicaemia or pneumonia can be fatal. Fortunately this is a rare complication of tetracycline therapy. Superinfection following the use of the tetracyclines emphasises that an antibiotic with a wide range of activity should not be prescribed if an appropriate 'narrow-spectrum' antibiotic is available. The tetracyclines quite commonly cause mild diarrhoea.

Pregnant women with pyelonephritis treated with tetracycline intravenously may develop severe liver damage. Staining of growing teeth and bone occurs and this could interfere with their growth and development in infants. Accordingly the use of tetracyclines is contraindicated in pregnancy and in childhood.

The tetracyclines can also exacerbate renal failure and should not be given to patients with renal disease.

Chloramphenicol

Chloramphenicol has a range of activity similar to that of the tetracyclines with the important difference that it is effective in enteric fever. It is more active than the tetracyclines against *H. influenzae* and is the antibiotic of choice in meningitis due to this organism. The daily dose for an adult is 1-3 g. Preparations for parenteral administration are also available. Chloramphenicol eye drops and ointment are indicated for purulent conjunctivitis.

ADVERSE EFFECTS

As with the tetracyclines, chloramphenicol may cause diarrhoea. Much more serious, although fortunately rare, are the blood dyscrasias which have been reported following its use. This antibiotic has in its chemical structure a benzene ring of the type known to cause bone marrow aplasia. Although pancytopenia due to chloramphenicol is very uncommon, it is almost invariably fatal and this antibiotic should be used systemically *only* for the treatment of typhoid fever and *H. influenzae* meningitis and in other conditions only on the very rare occasion when there is no alternative therapy.

Chloramphenicol should never be given to premature infants and very rarely to the newborn because of the risk of the development of the frequently fatal 'grey syndrome'. This is a state of peripheral circulatory failure caused by the very high blood levels of chloramphenicol due to its inadequate conjugation in the liver at this age.

The Lincomycins

Lincomycin and *Clindamycin* (7-chlorolincomycin) resemble erythromycin in activity and low toxicity and are effective against penicillinase-producing *Staph. aureus*. They penetrate well into bone and are therefore particularly useful in osteomyelitis and infective arthritis. The lincomycins are also the antibiotics of choice for the treatment of *Bacteroides* infections which cause local suppuration often related to the intestinal tract, e.g. pelvic abscess. The dose of lincomycin is 500 mg six-hourly and clindamycin 300 mg six-hourly.

Clindamycin is at least five times more active than lincomycin against staphylococci; it is given by mouth and is well absorbed from the gut. In contrast, lincomycin is irregularly absorbed and commonly causes diarrhoea but a parenteral preparation is available. Other side-effects are rare.

Sodium Fusidate

This sodium salt of fusidic acid is highly bactericidal against staphylococci and is useful in infections caused by penicillin-resistant organisms. Like the lincomycins it is well concentrated in bone. Sodium fusidate is given orally in doses of 250-500 mg thrice daily, is rapidly absorbed, attains high tissue levels and is reasonably well tolerated, although nausea and vomiting are not uncommon during therapy. An intravenous preparation is available. This antibiotic is expensive and is principally indicated for bone infections due to staphylococci which are resistant to the penicillins and the lincomycins.

The Aminoglycoside Antibiotics

Streptomycin, Kanamycin, Gentamicin, Neomycin, Framycetin and Tobramycin

These have similar chemical structures, pharmacological actions and adverse effects. They are not absorbed and for systemic treatment must be given by injection.

The outstanding property of *streptomycin* is its bactericidal effect on the tubercle bacillus. It is given in conjunction with para-aminosalicylic acid (PAS) and isoniazid and this triple therapy prevents the emergence of resistant strains. For long-term therapy the daily dose of streptomycin should not exceed 1 g. The chemotherapy of tuberculosis is discussed in detail on pages 366-371. Its use in infections due to Gram-negative bacilli is restricted by the rapid development of bacterial resistance. When infective endocarditis is due to an organism relatively resistant to penicillin, such as *Strept. faecalis*, good results may be obtained by combining streptomycin with large doses of benzylpenicillin or ampicillin.

Kanamycin is active against many Gram-negative bacilli and resistance develops much more slowly than with streptomycin. It should be reserved for the treatment of serious infection such as peritonitis or bacteraemia due to Gram-negative bacteria, e.g. *Esch. coli* or *Proteus* species. It is also used in the treatment of gonorrhoea due to organisms of reduced penicillin sensitivity. The dose should not normally exceed 250 mg six-hourly by intramuscular injection.

Gentamicin has a range of activity similar to kanamycin but has the very important additional advantage of being effective against *Ps. aeruginosa* (*Ps. pyocyanea*). It is also active against penicillin-resistant staphylococci but inactive against streptococci and most anaerobic organisms. The dose depends on renal function and the age and weight of the patient. Up to 5 mg per kilogram body weight per 24 hours in divided doses is required for serious infections but 2 mg per kg is sufficient for uncomplicated urinary tract infections. *Tobramycin* is a new aminoglycoside which is more active than gentamicin against *Ps. pyocyanea* and is possibly less ototoxic.

Neomycin is too toxic to be given parenterally but local applications containing neomycin are used in infections of the skin and eye. Neomycin is used for the pre-operative preparation of the large bowel and also in hepatic encephalopathy to reduce the numbers of colonic bacteria.

ADVERSE EFFECTS

The outstanding toxic effect of all the aminoglycosides is on the eighth cranial nerve. With streptomycin and gentamicin the vestibular division is initially affected with resultant vertigo and incoordination. Later, deafness may also occur. Kanamycin tends to cause deafness first while neomycin is much too ototoxic for systemic use. The ototoxicity of the aminoglycosides is directly proportional to the age of the patient, the serum level of the antibiotic and the duration of administration. The aminoglycosides are principally excreted from the body by the kidneys and the risk of ototoxicity is increased if there is any impairment of renal function. Consequently these antibiotics must be given with great caution to any patient with renal disease and where possible serum levels of the antibiotic should be monitored and the dose adjusted accordingly. Sensitivity rashes and fever occur in about 5 per cent of patients treated with streptomycin. Desensitisation is indicated if it is essential to continue with the antibiotic (p. 368). Application of neomycin to the skin may cause hypersensitivity.

Cycloserine

Cycloserine is a bactericidal antibiotic used in the treatment of urinary tract infections due to *Esch. coli*. The adult dose is 250 mg orally twice daily for a fortnight. Overdosage or normal dosage in the presence of impaired renal function may cause drowsiness or epilepsy. Recurrent urinary tract infection with *Esch. coli* may be prevented by long-term treatment with 125-250 mg cycloserine on alternate days.

The Polymyxins

The most important member of this group of antibiotics is polymyxin E (Colistin). It is bactericidal against many Gram-negative bacilli and all strains of *Ps. aeruginosa*.

Colistin sulphomethate. This is given by intramuscular injection in a dose of 1-3 million units eight-hourly depending on the weight of the patient and renal function. Colistin is sometimes prescribed orally in *Esch. coli* gastroenteritis of infants but the principal indication is pseudomonas infections of the renal tract. All polymyxins are nephrotoxic and may also cause paraesthesiae and dizziness although these side-effects are rare with colistin.

Nitrofurantoin and Nalidixic Acid

These two unrelated chemotherapeutic agents are indicated only for the treatment of infections of the urinary tract and are not effective in other conditions. They are active against the common Gram-negative bacilli such as *Esch. coli* and Proteus and are administered by mouth. The dose of nitrofurantoin is 100 mg three or four times a day and that of nalidixic acid 1 g three times a day. Nausea and vomiting are common during nitrofurantoin therapy while photo-sensitivity skin reactions occasionally occur with nalidixic acid. Both drugs are potentially neurotoxic. Nitrofurantoin can cause peripheral neuropathy especially if there is renal failure and nalidixic acid may produce increase in intracranial pressure in babies.

Antibiotics effective against Fungi

The Polyene Antibiotics

Nystatin. Nystatin is effective against *Candida albicans*, a normal inhabitant of the mouth and intestine which may cause thrush particularly in debilitated, diabetic or pregnant patients. Thrush infections also commonly occur in patients receiving corticosteroid or cytotoxic drugs or wide range antibiotics such as tetracycline. Nystatin is not absorbed when given by mouth and cannot be administered parenterally as it has a very low solubility. Oral, oesophageal or intestinal thrush may be treated with tablets of 500,000 units of nystatin which are sucked four times daily for about a week. Pessaries are available for the treatment of vaginal infections and are inserted once or twice daily. Local treatment with nystatin is no better than the very cheap but unsightly 1 per cent aqueous solution of gentian violet.

Amphotericin B. This is indicated only for the treatment of severe systemic fungal infections such as coccidioidomycosis, histoplasmosis and invasive candidiasis. It is given in gradually increasing doses by intravenous injection and is very toxic causing fever, nausea, vomiting, local thrombophlebitis and rise in blood urea.

There are over 50 polyene antibiotics but apart from nystatin and amphotericin B only *Candicidin* and *Natamycin* have any clinical application, the former in vaginal thrush and the latter in aspergillosis (p. 372).

Griseofulvin

This antibiotic is effective by mouth in dermatophytic infections such as ringworm of the skin, hair and nails, where griseofulvin appears to be taken up by newly formed keratin which is then resistant to further invasion by the fungus. Superficial skin lesions respond promptly but many months of treatment may be required to eradicate the infection from slowly growing tissues such as the nails. The antibiotic is given in doses of 250 mg (child) to 500 mg (adult) daily and is well tolerated. It may cause light sensitivity.

Other Anti-fungal Agents

Clotrimazole and *5-Fluorocytosine* are two new anti-fungal drugs which are being investigated at the present time.

Antitubercular, Antileprotic and Antiprotozoal Preparations

Drugs other than streptomycin used in the treatment of tuberculosis include para-aminosalicylic acid, isoniazid, ethambutol, thiacetazone and rifampicin. These are discussed on page 367.

The chemotherapy of leprosy and protozoal infections is described in the section on tropical diseases. The use of metronidazole (Flagyl) in the treatment of vaginitis and urethritis due to *Trichomonas vaginalis* is described on page 80. It is also valuable in amoebiasis (p. 970) and ulcerative stomatitis (p. 444).

Antiviral Chemotherapy

The success of antibacterial chemotherapy has not been matched in viral diseases where only a very few infections are at the present time susceptible to drug therapy. Due to the relatively long incubation period of many viral infections, replication of the virus is almost complete before clinical features appear, maximal cell damage has occurred and the disease is well advanced. The intracellular position of the micro-organism further complicates chemotherapy. There are, however, three compounds of proven therapeutic efficacy.

Idoxuridine. Idoxuridine interferes by competitive inhibition with viral DNA metabolism and is effective in the treatment of infections caused by viruses of the herpes group. It is used topically in *Herpes simplex* infections of the cornea, skin and genitalia and has been administered systemically in *H. simplex* encephalitis. Idoxuridine is also used in the treatment of herpes zoster where frequent local applications to the rash appear to reduce the duration of the skin lesions and decrease the incidence of post-herpetic neuralgia. It is an expensive drug.

Cytarabine. This also acts on viral DNA and has been used for the treatment of disseminated *H. simplex* infections and severe attacks of shingles such as generalised zoster and zoster encephalitis.

Methisazone is effective in the prophylaxis of smallpox and has been used in complications of smallpox vaccination (p. 92).

Selection of Antimicrobial Agent

In addition to knowledge about the properties of the available antimicrobial agents important considerations in the choice of effective chemotherapy are:

1. The nature and site of the infection.
2. Adverse effects.
3. Factors determining the resistance of organisms to antimicrobial agents.
4. Cost.

1. Selection of Antimicrobial Agent in Relationship to the Nature and Site of the Infection

In instances where the nature of the infection can be reliably predicted from the clinical features of the illness, treatment can proceed without isolation of the causative organism. For example, acute follicular tonsillitis and lobar pneumonia are sufficiently characteristic on clinical examination to allow the causative organism and its antibiotic sensitivity to be assumed with a high degree of probability and the appropriate antibiotic (penicillin) given. In acute exacerbations of chronic bronchitis the causative organisms are almost always pneumococci and *Haemophilus influenzae* and the use of ampicillin or co-trimoxazole is indicated without specific laboratory diagnosis.

Where there is uncertainty about the nature of the infection a bacteriological diagnosis should be made so that the appropriate antibiotic can be given. If the organism is one such as *Strept. pyogenes*, which has a predictable susceptibility to the generally used antimicrobial agents, no further laboratory sensitivity tests are necessary.

Sensitivity tests will be required for a minority of bacteria known to vary in their susceptibility to antimicrobial agents. This is necessary for example in staphylococcal infections and in infective endocarditis. Once the sensitivity of the organism has been determined, it is relatively rare for this to change in the course of treatment. It must be stressed that there is not a complete correlation between the results of sensitivity tests and the response to chemotherapy and sometimes clinical judgement may indicate a different drug from that recommended by the bacteriologist.

When several antimicrobial agents are available for the treatment of an infection it is usual to select the one that is bactericidal in order that the organisms are killed rapidly; bacteriostatic drugs suppress the growth of the organism while the natural defence mechanisms of the body dispose of it. The choice is probably of no great significance in the majority of infections but may be important in the treatment of bacteraemia and in patients with deficient defence mechanisms.

The use of two or more antibacterial drugs is occasionally of proven value. Thus in tuberculosis three agents are prescribed so as to reduce the emergence of resistant strains. Combinations of antibiotics with differing ranges of activity may also be used to treat infections due to more than one species of microorganism or where it is believed that the effect of the combination of drugs is more potent than an equivalent amount of any one of the compounds acting alone. This has been described as 'synergy'; an example of this is the combination of trimethoprim with sulphamethoxazole as co-trimoxazole. Unfortunately there have been relatively few clinical trials which have compared the efficacy of combinations of antibiotics with single drugs so that the use of combinations remains somewhat empirical. Whenever possible their choice should be specifically directed by bacteriological diagnosis and accompanying sensitivity tests.

While details of therapy are given when individual diseases are described, the principles involved in the management of bacteraemia and of infection of the main systems are outlined here.

The Chemotherapy of Bacteraemia. In many patients in whom bacteraemia is suspected, treatment must be started without any knowledge of the causative organism or its susceptibility to antibacterial drugs as delay in instituting treatment while awaiting a bacteriological diagnosis may lead to the death of the patient. Initially therefore antimicrobial therapy must cover both Gram-positive and Gram-negative organisms and either a wide range antibiotic or a suitable combination of agents may be employed. The cephalosporins and gentamicin have a wide range of activity and can be given singly. Alternatively ampicillin (500 mg six-hourly) plus cloxacillin (1 g six-hourly) can be used. Gentamicin combined with penicillin or lincomycin is valuable for the treatment of fulminating undiagnosed infections such as suspected septicaemia in patients with a poor resistance, e.g. those suffering from leukaemia.

Kanamycin is very effective in a dose of 250 mg six-hourly when Gram-negative bacilli other than *Ps. aeruginosa* are involved. If there is impairment of renal function, care must be taken to avoid accumulation of the antibiotic in the blood with potential ototoxicity. Providing the blood urea is normal, a dose of 250 mg six-hourly is usually safe, but in cases of doubt, serum assay of the antibiotic should be carried out one hour after a dose. The serum level in such specimens should not exceed 20 micrograms per ml and the frequency of the dose must be regulated to ensure that this is so. Gentamicin may be used instead of kanamycin in a dose of up to 5 mg per kg per day and is of particular value in infections due to *Ps. aeruginosa* or *Staph. aureus* which are highly susceptible to this antibiotic. If renal function is impaired or high doses of gentamicin are being given, serum levels should be measured and should not exceed 10 micrograms per ml.

Where Gram-positive cocci are the cause of the infection, benzylpenicillin should be given if the organism is known to be sensitive to penicillin. Flucloxacillin is indicated if penicillinase-producing staphylococci are responsible for the infection. If the patient is allergic to penicillin or the organism is resistant to cloxacillin, the next choice would be lincomycin.

Following the identification of the infecting organism and its antibiotic sensitivity, the drug or combination of drugs specifically indicated should be given along with other measures for the treatment of circulatory failure, dehydration and intravascular coagulation.

Chemotherapy of Infections of the Heart. The prophylactic use of antimicrobial agents in general is undesirable but notable exceptions to this are their uses in the prevention of rheumatic fever (p. 262) and infective endocarditis (p. 265).

The treatment of infective endocarditis exemplifies the management of deep-seated infection by the identification of the causative micro-organism together with the use of sensitivity tests and the administration of antibiotics in large dosage, or in combination when dealing with a refractory organism.

Chemotherapy of Infections of the Respiratory System. Many acute infections of the upper respiratory tract are due to viruses which are not affected by the antimicrobial agents in general use. Laboratory diagnosis is helpful in establishing whether or not there is a bacterial cause.

Penicillin is indicated for streptococcal and pneumococcal infections. In many cases of acute lobular pneumonia and acute exacerbations of chronic bronchitis, pneumococci and *H. influenzae* are responsible and treatment with either ampicillin, tetracycline or co-trimoxazole is indicated. Less commonly, other bacteria are involved necessitating sputum culture and determination of sensitivity, e.g. *Staph. aureus*, *Klebsiella pneumoniae* and *Ps. aeruginosa*. This subject is discussed further on page 352.

Chemotherapy of Intestinal Infections. Bacterial resistance is readily induced by the indiscriminate use of antimicrobial agents in infections of the gut. Specific therapy is usually not required in bacillary dysentery due to Shigella and in gastroenteritis due to type-specific *Esch. coli*. When it is indicated by the presence of systemic upset, local knowledge of sensitivity is important as resistance may have been acquired to one or more of the antibacterial agents commonly used in that area. Most forms of food poisoning due to salmonella similarly do not require specific chemotherapy but severer attacks may be associated with bacteraemia and must be treated, usually with ampicillin.

Chemotherapy of Infections of the Urinary Tract. The principles involved are the clinical and bacteriological recognition of the infection and the short or long-term use of specific chemotherapy. Even appropriate drugs cannot be effective if there is an obstructive lesion of the urinary tract and this must be diagnosed and treated when infection is persistent or recurrent.

The majority of uncomplicated urinary tract infections in domiciliary practice are caused by sulphonamide sensitive *Esch. coli* strains and sulphadimidine is effective in these patients. In chronic, recurrent or hospital acquired infections urine should be sent for culture and treatment started with ampicillin while awaiting the result.

In chronic pyelonephritis long-term suppressive therapy may be required and cycloserine and ampicillin are particularly valuable for this purpose. With protracted therapy, periodic changes may be made in the drugs used, particularly if problems arise from adverse effects or from superinfection with antibiotic-resistant organisms or when it is impossible to monitor the infection adequately. This last difficulty may also occur in prostatitis because of the inaccessible site of the infection and prolonged treatment with ampicillin, co-trimoxazole or erythromycin may be necessary on an empirical basis.

As with other drugs antibiotics must be used with special care in the presence of renal failure.

Chemotherapy of Infections of the Nervous System. If an antimicrobial agent is to be effective, it must come in contact with the infected tissues. A walled-off abscess in the brain, as in the lung or pleural cavity, may be inaccessible to chemotherapy. In the case of the nervous system another difficulty is presented by the 'blood-brain barrier' whereby a drug like penicillin may be prevented from reaching the brain. However, the presence of inflammation facilitates its diffusion into the cerebrospinal fluid and nervous tissues and intrathecal administration of penicillin is very seldom necessary in meningitis. If penicillin is given by this route, the dose must *never* exceed 20,000 units (10,000 units in children) as fatal encephalopathy may ensue. Pneumococcal and meningococcal meningitis are treated with systemic benzylpenicillin and meningitis caused by *H. influenzae* with chloramphenicol. Cerebral abscesses may be due to mixed organisms and cephaloridine is the treatment of choice.

Prophylactic Chemotherapy. There are relatively few *absolute* indications for prophylactic chemotherapy. In general, prophylaxis with antimicrobial agents should be carried out only against known organisms of predictable sensitivity, whenever possible with an antibiotic of narrow range, usually penicillin. Examples of prophylaxis with the penicillins are given on pages 96 and 97.

Prophylactic antibiotics should not be given to unconscious patients or used to cover clean surgical operations as there is no evidence that they are beneficial and positive harm may result from superinfection with resistant organisms or from side-effects of the antibiotic.

2. Selection of Antimicrobial Agents in Relation to Adverse Effects

Before prescribing an antimicrobial agent it is very important to ensure that it is unlikely to harm the patient. Enquiry should be made about any previous allergic reactions, particularly with the penicillins. Pregnant women and children should not be given tetracyclines. Co-trimoxazole is also best avoided in pregnancy and this compound, together with other sulphonamides, must not be given to patients with glucose-6-phosphate dehydrogenase deficiency as haemolysis may be precipitated. Chloramphenicol should not be prescribed unless there is no available alternative and it is contraindicated in the neonate. Ampicillin must not be given to patients suffering from glandular fever and the aminoglycoside antibiotics should be used with caution in patients with renal disease and in the elderly.

3. Factors Determining the Resistance of Organisms to Antimicrobial Agents

Antibiotic resistance may be an intrinsic character of the micro-organism. Of greater clinical importance is the acquisition of resistance to many antimicrobial drugs by the mechanisms described on page 44. It occurs particularly with staphylococci, Gram-negative coliform bacilli and tubercle bacilli; in the case of organisms such as *Strept. pyogenes* and *Strept. pneumoniae* it develops to a limited number of agents such as the tetracyclines. In these instances the possibility of the occurrence of resistant organisms must particularly be kept in mind. In the case of *Mycobacterium tuberculosis* this is counteracted by the simultaneous use of two or more drugs, as it is improbable that organisms resistant to two different antibacterial agents will appear at the same time. The use of three drugs makes the chances virtually nil.

4. Cost

The chemotherapy of infections can be very expensive, especially when newly introduced preparations are used. Enquiry should be made about price before unusual antibiotics are prescribed as the difference in cost can be over a hundred-fold.

Conclusion

General Principles in the Use of Antimicrobial Agents

1. Antibiotics must not be prescribed unless absolutely necessary. They should not be given for trivial infections such as minor skin sepsis or gastroenteritis and, with very few exceptions (p. 105), they are ineffective in viral disease.

2. Serious infections should be treated whenever possible with bactericidal as opposed to bacteriostatic preparations and initially with parenteral agents. Although the average recommended dose of an antibiotic is sufficient for the

treatment of the majority of infections, higher dosage may be necessary for serious infections.

3. Many acute infections such as streptococcal tonsillitis and pneumococcal pneumonia which are caused by organisms of predictable sensitivity can be treated without assistance from the laboratory. Laboratory aid is however required for bacteraemia, recurrent infections and those caused by less common pathogens.

4. Well established and usually cheaper antibiotics are preferable to new and generally more expensive preparations unless there is some commanding reason to choose otherwise.

5. Antibiotics with a relatively limited range of activity such as benzylpenicillin are preferable to broad-spectrum compounds like tetracycline, so as to reduce the danger of superinfection.

6. There are very few indications for combinations of antibiotics (p. 106) or prophylactic antibiotics (p. 107).

7. Many adverse effects and even death may result from the use of antibiotics, and their careless prescription is to be deplored.

E. B. French.
A. M. Geddes.
J. C. Gould.

Further reading:

Christie, A. B. (1974). *Infectious Diseases: Epidemiology and Clinical Practice*, 2nd ed. Edinburgh and London: Churchill Livingstone.

Cruickshank, R. (1973). *Medical Microbiology*, 12th ed. (vol. 1) (vol. 2, 1974). Edinburgh and London: Churchill Livingstone.

Garrod, L. P., O'Grady, F. & Lambert, H. P. (1973). *Antibiotic and Chemotherapy*, 4th ed. Edinburgh and London: Churchill Livingstone.

Note:

The British National Formulary (1974-76) should be consulted for further information about drugs and the names of proprietary equivalents.

Nutritional Factors in Disease

THAT disease might be due to lack of some essential factor had little place in the thinking of 50 years ago. Consequently the concept of deficiency diseases, nutritional and endocrine, grew in the present century. As deficiency diseases came to be recognised and understood, the next step was the realisation that lack of nutritional and endocrine factors affects primarily the chemistry of the body. Disease resulting from a 'biochemical lesion' and structural changes are late effects, secondary to change in function.

This revolution in medical thought had profound practical consequences. The great nutritional diseases that flourished within the lifetime of some doctors still in practice have now vanished wherever medical knowledge has been linked with proper administration of food supplies. Florid rickets is now a clinical curiosity in Britain, yet in the streets of our big cities we still see elderly people, bandy-legged, stunted and pigeon-chested, who carry the scars of it. Pellagra, prior to 1940, affected tens of thousands of poor country people in the southern states of the USA; better knowledge of nutritional needs and, above all, improved economic circumstances have largely swept it away. The classic nutritional diseases occur only in situations where there is a failure both of food supplies and medical care which regrettably is still the case in many parts of the world. Even in the USA, the richest country in the world, probably several million people are suffering from undernutrition or malnutrition. Those particularly liable to be affected are Negroes, Indians and 'poor whites' who, because of lack of education, physical or mental handicaps, alcoholism or drug addiction, are unable to obtain regular employment. It is these classes of people all over the world who tend to have large families and it is not surprising that nutritional disorders are especially liable to develop in the fourth and subsequent children.

Even in times of severe food shortage, proper application of medical knowledge can do much to overcome the worst effects of qualitative dietary deficiencies; medicine can deal with beriberi, scurvy and pellagra, but has no direct means of treating the effects of underfeeding—undernutrition. Consequently lack of sufficient food continues to be a most serious cause of ill-health in many underdeveloped regions.

The present world population is estimated to be more than 3,500 million and increasing by 70 million per year. In the absence of major catastrophes there will be more than twice as many inhabitants in the world by the year 2000 as there are today. This is not due to an increase in human fertility but is caused almost entirely by a remarkable reduction in the death rate. The greatest threat to the well-being of mankind is this explosive population growth rate. One-third of the world's population receives less than 2,000 kcal/head/day. Agricultural production is hampered by bad climates, soil erosion, lack of fertilisers, antiquated farming methods, political upheavals and war. This situation will steadily deteriorate unless national programmes of population control and family planning based on modern contraceptive techniques are evolved and effectively put into operation. In addition, food production must be greatly increased by the use of high-yielding strains of rice, wheat and maize.

Aetiology of Nutritional Disorders

There are five essential causes of nutritional disorders:

1. *Quantitative Dietary Deficiency.* Not enough food results in undernutrition or when more severe, frank starvation.

2. *Qualitative Dietary Deficiency.* Wrong food results in malnutrition. The term 'malnutrition' should be restricted to those nutritional disorders, e.g. rickets and scurvy, which are due to lack of specific chemical components (nutrients) of a proper diet.

3. *Quantitative Overnutrition.* Too much food results in obesity.

4. *Qualitative Overnutrition.* This is due to too much of one food component, e.g. hypervitaminosis D.

5. *Effects of Natural Toxins in Foods.* Some foods contain small amounts of toxic substances which can lead to disease if a person or community has to rely too heavily on a single foodstuff, e.g. lathyrism (p. 169).

Social and Economic Causes of Nutritional Disorders. Even in countries where food, ample in quantity and quality, can be purchased, nutritional disorders arise because of poverty, prejudice, ignorance or bad housekeeping often caused by bad housing. The old, the solitary and children are most often affected.

Pathological Causes of Nutritional Disorders. Even with an ample income, an adequate home and a knowledge of dietetics, a patient may develop a nutritional disorder through some other disease which 'conditions' (facilitates) it in one or more of the following ways.

DEFECTIVE INTAKE OF FOOD. (*a*) *Loss of appetite* may be an important symptom of organic disease, e.g. cancer of the stomach, and also of psychogenic disease, e.g. anorexia nervosa. (*b*) *Persistent vomiting* from any cause. (*c*) *Food fads*, e.g. in very strict vegetarians (vegans). (*d*) *Alcohol* provides calories but no essential nutrients. Chronic alcoholics suffer from malnutrition more often than undernutrition. (*e*) *Unbalanced therapeutic diets*, e.g. diets for digestive diseases may lack ascorbic acid unless care is taken to provide it. (*f*) *Prolonged parenteral feeding* with intravenous glucose after surgical operations may precipitate acute deficiencies of the vitamin B complex.

DEFECTIVE DIGESTION AND ABSORPTION. (*a*) *Achlorhydria* is a contributory factor in the causation of iron deficiency anaemia. (*b*) *Steatorrhoea* limits the absorption of fat-soluble vitamins and calcium. (*c*) *Intestinal hurry* due to surgical short circuits, etc. may impair digestion. In starving people the ingestion of unsuitable foods often causes intestinal hurry and intensifies their plight. (*d*) *Antibiotics*, if their administration is prolonged, may interfere with the production of vitamins synthesised by intestinal bacteria.

DEFECTIVE UTILISATION. (*a*) *Cirrhosis* of the liver may interfere with the proper utilisation of ingested nutrients, e.g. of protein and vitamin K. (*b*) *Malignancy*, in some unknown way, may produce a state of undernutrition despite an adequate diet. The same may be true of tuberculosis and other prolonged infections. (*c*) In *renal failure* vitamin D is not converted to the active metabolite (p. 136). (*d*) Some *drugs*, e.g. anticonvulsants, are antagonists of folate and of vitamin D.

LOSS OF NUTRIENTS FROM THE BODY. (*a*) In the *nephrotic syndrome* there is loss of protein in the urine. (*b*) In *diabetes mellitus* uncontrolled glycosuria causes undernutrition. (*c*) In *excessive menstrual bleeding* (menorrhagia) secondary iron deficiency anaemia is common. (*d*) In severe or chronic *diarrhoea* potassium is lost.

INCREASED NUTRITIONAL NEEDS. (*a*) In pregnancy, lactation and adolescence (especially after an illness in the last named), and for those engaged in hard physical work, particularly in cold climates, the usual diet may be insufficient. (*b*) In fevers and hyperthyroidism the increased metabolism calls for more calories. (*c*) After burns, fractures and major surgery, there is an increased catabolism of protein and ascorbic acid which cannot be replaced until convalescence begins.

Although nutritional disorders are often precipitated and sometimes caused by such conditioning factors, the prime cause is usually a diet deficient in one or more nutrients. It is therefore poor practice to prescribe a single nutrient (e.g. a vitamin) without first looking for evidence of other deficiencies and thereafter taking measures to improve the diet.

QUANTITATIVE DIETARY DEFICIENCY

Requirements for calories vary widely, even among apparently similar individuals. 'Recommended Allowances' provide only an approximation for an individual.

The UK Department of Health and Social Security recommended in 1969 that 3,000 kcal is adequate for a moderately active man and 2,200 kcal for a moderately active woman. Slightly lower figures are recommended by the Food and Nutrition Board of the USA. The Royal Society (London) recommends (1972) that joules, which are S.I. units (p. 1008), should replace calories which are not. One calorie = 4·184 J so 3,000 kcal = 12,550 kJ or 12·6 MJ.

The population of Britain, including infants, children and adults, probably needs an overall average *intake* of 2,500 kcal/head/day. In order that the population may actually consume this amount, the food retailed in the shops must provide more to allow for household wastage. The food supplies of Britain ordinarily provide around 3,000 *retail* kcal/head/day. It is this shop-value of our food supplies that is sometimes discussed in Press and Parliament and often confused with average physiological requirements.

Undernutrition and Starvation

Starvation may conveniently be defined as undernutrition of sufficient severity to warrant in-patient treatment in hospital; the body weight may be reduced to 75 per cent of normal or less.

Undernutrition and starvation arise (1) when there is not enough food to eat, for instance in times of famine, (2) when there is severe disease of the digestive tract, preventing the absorption of nutrients, as in the malabsorption syndrome and cancer of the oesophagus or (3) when there is a toxaemia which prevents normal metabolism of nutrients by the tissues often with anorexia also, e.g. in renal or hepatic failure or in severe and long-continued infections. In all these circumstances there is wasting of the body with much loss of both muscle and fat. This gives rise to a clinical picture with an underlying morbid anatomy and chemical pathology which is essentially similar whatever the primary cause.

Clinical Features. When the caloric value of the diet is inadequate, adults lose weight, and children cease to grow or even lose weight. The loss may be rapid at first, but tends to slow down and become stabilised at a lower level because the body is able to adapt itself, at least partly, to an insufficient intake of food. This adaptation is possible because (*a*) the bulk of the muscles and glands is reduced in size, requiring less energy for their maintenance, (*b*) the basal metabolism of the tissues is reduced, (*c*) the body, being lighter, requires less mechanical work to move it about, and (*d*) unnecessary voluntary movements are curtailed.

The patient becomes thin and the skin lax, most noticeably over the upper arm and abdomen. The skin is thin, dry, inelastic and often cyanosed at the extremities. The hair becomes dull, dry and inflexible ('staring' hair). The eyes are dull and sunken, yet the wasting of orbital tissues may give them an unusual prominence. The heart is reduced in size and there is often bradycardia and a reduced systolic blood pressure. Atrophy of the small intestine is always present in starvation and may be severe; in which case the inability to digest and absorb nutrients will greatly prejudice the chances of recovery. In severe cases once diarrhoea has begun, the loss of fluid in the stools causes grave disturbances in water and salt balance. Loss of body water is a characteristic immediate response to calorie restriction. Its cause is not known. It may amount to as much as 4 kg. It is replaced rapidly once a normal intake is resumed. This phenomenon probably explains why reducing diets for obesity are so successful for the first few days.

Eventually, dependent 'famine' oedema begins to appear. This results from prolonged intake of insufficient food. It is often preceded by a period of nocturnal polyuria. Famine oedema is not necessarily associated with any fall in the level of plasma proteins, but is due rather to wasting of tissues without a corresponding loss of body water. A mild normocytic, normochromic anaemia is common, due to a reduction in the red cell population without corresponding alteration in the plasma volume.

Seriously underfed patients are weak and sometimes suffer from attacks of syncope. Hypothermia should be looked for with a low-reading thermometer. Psychological symptoms frequently occur in starving people. Mental restlessness, irritability and indifference to the troubles of others may be combined with physical apathy. Undernourished individuals are susceptible to infections like bronchopneumonia as well as to diarrhoea and starving groups in famines have often had high mortalities from epidemics, e.g. of typhus or cholera.

Diagnosis. In times of famine the signs of starvation may be all too obvious, so much so that other causes of emaciation can be overlooked. However, a similar clinical picture may be produced by the cachexia of advanced cancer, tuberculosis, dysentery or other severe chronic infections. It is also seen in young children with protein calorie malnutrition (PCM, p. 117).

Famine oedema must be distinguished from other primary causes of oedema—cardiac, renal or hepatic and from the oedema of PCM and beriberi. The diagnosis of undernutrition depends on (*a*) careful enquiry into the social, economic and dietary history and a knowledge of local food conditions, and (*b*) evidence of recent weight loss and the other clinical features mentioned above.

The severity of the starvation can be assessed by working out the patient's weight for height as a percentage of the estimated normal for the population (Table 18, p. 1007). Starvation is severe and dangerous when weight is less than 70 per cent of normal.

Treatment. In mild undernutrition, all that is needed is suitable food. Its management is more an administrative than a medical problem. When the patient suffering from starvation is seriously ill the nature of the treatment depends essentially on the facilities available.

Most famine victims, because of alimentary dysfunction, cannot deal with large quantities of food. The patient's desire for food may be immense and no guide to his digestive capacities. Limitation of the food intake is essential if there is nutritional diarrhoea or a severe degree of nutritional cachexia.

The choice of food is difficult. In advanced cases only bland foods can be tolerated by the thin-walled intestines lacking essential digestive enzymes. One of the best foods is skimmed milk, reconstituted from dried powder to give a 10-15 per cent mixture. Frequent small feeds, 100 ml or so at a time (as often as the patient is willing and able to take them) is the best way of averting death. This requires constant personal attention and nursing care. A variety of mild flavouring essences may be useful for improving the appetite and a compound vitamin syrup added. As the patient begins to recover he should be encouraged gradually to take semi-solid foods, along the lines followed in weaning a baby. It is advisable to give foods with which the patient is familiar. With re-feeding there may be some increase in oedema, unless the supply of salt is restricted.

There may come a time when a patient with severe starvation refuses all food, although fully rational. The outlook is then very grave. Feeding of milk and other fluids through a stomach tube then provides the only hope. Spectacular improvement may follow this measure, but some patients are beyond recovery.

Prognosis. Physical and psychological recovery is usually complete if sufficient calories are provided for cases of primary undernutrition. When irreversible changes have developed in the heart and small intestine, as occurs in severe starvation, the prognosis is poor.

Prevention. This rests with the social, economic and agricultural legislators and executives. Famines from crop failure can be greatly alleviated by advanced contingency planning. Those caused by a natural disaster like an earthquake are unexpected: the outcome depends on how well the country's administration stands up to the strain. Famines resulting from war are the most difficult. The problems of prevention and relief of famine are discussed in a book published by the Swedish Nutrition Foundation (p. 184).

QUALITATIVE DIETARY DEFICIENCY

Energy-yielding Nutrients

Carbohydrates. These usually provide the greater part of the calories in a normal diet, but no individual carbohydrate is an absolute dietary necessity in the sense that the body needs it but cannot make it for itself from other nutrients. If the carbohydrate intake is less than 100 g per day ketosis is likely to occur.

Fats. With their high caloric value, fats are useful to people with a large energy expenditure; moreover they are helpful in cooking and making food appetising. Though rats need linoleic or arachidonic acids in their diet, deficiency of these *essential fatty acids* is rare in man. It has been demonstrated in patients who have been fed intravenously for long periods without fat emulsions.

The possible role of cholesterol, fats and different fatty acids in the pathogenesis of atherosclerosis and coronary thrombosis is discussed on page 265.

Proteins. Proteins provide amino acids, of which eight are essential for normal protein synthesis and for maintaining nitrogen balance in adults. These are termed *essential amino acids* because the body cannot make them for itself and so must obtain them from the diet. They are methionine, lysine, tryptophan, phenylalanine, leucine, isoleucine, threonine, and valine. There is evidence that histidine and perhaps arginine are needed for growth in infants.

The 'biological value' of different proteins depends on the relative proportions of essential amino acids they contain. Proteins of animal origin, particularly from milk, eggs, meat and fish, are generally of higher biological value than the proteins of vegetable origin. Most vegetable proteins are deficient in one or more of the essential amino acids; but it is possible to have a diet of mixed vegetable proteins with high biological value if the principle of *supplementation* is used. For example cereals, e.g. wheat, contain about 10 per cent protein and are relatively deficient in lysine. Legumes contain around 20 per cent of protein which is relatively deficient in methionine. If two parts of wheat are mixed (or eaten) with one part of legume, a food results which contains 13 per cent of a protein of high biological value. This happens because cereals contain enough methionine and legumes enough lysine to supplement the other component of the mixture.

A deficient intake of protein leads to (*a*) negative nitrogen balance; (*b*) wasting of tissues; and (*c*) fall in plasma albumin. For further information see page 118.

The usual recommended allowance for an adequate protein intake is 10 per cent of the total calories. The minimum requirement is less, around 40 g per day of good biological value protein for an adult.

PROTEIN-CALORIE MALNUTRITION

(PROTEIN-ENERGY MALNUTRITION)

Aetiology and Classification. Protein-calorie malnutrition (PCM) in early childhood is now regarded as a spectrum of disease. At one end there is *kwashiorkor* in which the essential feature is deficiency of protein with relatively adequate calorie intake. At the other end is *nutritional marasmus* (p. 123) which is total inanition of the infant, usually under 1 year of age, and is due to a severe and prolonged restriction of calories and protein as well as other nutrients. In the middle of the spectrum is *marasmic kwashiorkor* in which children have some clinical features of both disorders.

TABLE 1

Classification of PCM

	Body weight as percentage of international standard for age	Oedema	Deficit in weight for height
Kwashiorkor	80-60	+	+
Marasmic kwashiorkor	< 60	+	+ +
Marasmus	< 60	0	+ +
Nutritional dwarfing	< 60	0	minimal
Underweight child	80-60	0	+

Based on Joint FAO/WHO Committee on Nutrition. 8th Report, 1971 (with modifications in weight/height column).

Some children adapt to prolonged calorie and/or protein shortage by *nutritional dwarfism*. The most prevalent of all the varieties of PCM is *mild to moderate PCM* or the Underweight Child (see Table 1).

Children with one form of PCM often shift to another form. Thus a child with mild to moderate PCM may develop kwashiorkor after an infection. When such a child is treated and loses oedema he may look marasmic.

The incidence of PCM in its various forms is high in India and South-east Asia, in most parts of Africa and the Middle East, in the Caribbean Islands and in South and Central America. PCM is the most important dietary deficiency disease in the world, affecting tens of millions of children; hence it will be described in considerable detail.

Kwashiorkor

Cicely Williams in 1933 was the first to record that 'some amino acid or protein deficiency' might be an aetiological factor in kwashiorkor, the name given to this disease by the Ga tribe living in and around Accra, the capital of Ghana.

Aetiology and Incidence. Kwashiorkor typically arises when, after prolonged breast feeding, the child is weaned on to a traditional family diet, which is low in protein such as cassava, plantain or yam or a cereal diet which is refined and diluted (Fig. 18, p. 124). There is little or no milk and custom, sometimes reinforced by taboos, determines that the limited supply of foods of animal origin is given to the men of the family. In many rural areas, where kwashiorkor is endemic, the food supply becomes scarce each year before the harvest; at this 'hungry season' the incidence of kwashiorkor and other nutritional diseases increases.

If the customary diet of a population is limited in protein and in calories to around the levels of minimum requirements, a child may be in moderate health until his protein requirements are raised by an infection (Fig. 18). Gastro-enteritis, measles and malaria are all notorious precipitating causes of kwashiorkor.

Pathology. The insufficient supply of amino acids leads to inadequate protein synthesis, which impairs tissue replacement and development of organs and reduces synthesis of enzymes and plasma proteins. Some enzymes and tissues are more severely affected than others, particularly those with a rapid turnover.

The total protein content of the body may be as low as 60 per cent of normal for height, while the water content is increased. The failure to synthesise plasma albumin reduces the concentration to around 1·5 g/100 ml. By contrast the plasma gamma globulin is usually well maintained. A failure to synthesise digestive enzymes is frequently present, including those secreted by the mucosa of the small intestine (especially lactase) and by the pancreas. This may be partially responsible for the gastrointestinal upsets and diarrhoea which are so commonly present and which cause marked electrolyte disturbances due to loss of potassium and magnesium in the stools. Dietary deficiency of protein results in a failure to maintain the normal structure of the liver and muscles. The protein content of the liver is greatly reduced, while the lipid content is much increased.

Clinical Features. *Failure of Growth.* This is a constant and essential feature of the disease. The child's weight is usually well below standard for his age (Table 17, p. 1006) but the deficit may be masked by oedema.

Oedema. This may be slight or gross depending partly on the degree of protein deficiency but also partly on the salt and water balance. It usually affects the dorsum of the feet but may affect the hands and face as well. Ascites and pleural effusions are usually slight and, if detected clinically, suggest the presence of an infection such as tuberculosis.

Muscles and Fat. The muscles are wasted. This is particularly noticeable around the chest and the upper arm; the wasting of the legs and around the hips is frequently concealed by oedema. If the disease has resulted from a dietary restriction of both calories and protein, muscle wasting and an almost complete lack of subcutaneous fat is the most striking feature, but the feet are oedematous ('marasmic kwashiorkor'). Subcutaneous fat is often plentiful in children whose diets have provided ample calories but little protein.

Mental Changes. The child is apathetic and miserable.

Hair. This is nearly always affected in African children; in Asiatics the changes are less frequent. There is an alteration in texture. The hair becomes fine, straight and soft and is often sparse. The hair of African children may show a variety of pigmentary changes. Shades range from brown and reddish to grey, blond or even white. The extent of these changes in the hair is not an indication of the severity of the disease. They are sometimes pronounced in children who have been unwell for a long time but never seriously ill. Children with long straight black hair may show a pale band across the hair, corresponding to an earlier episode of kwashiorkor. This is the 'flag sign'.

Skin. Alterations in the skin are usually present, especially in severe cases. These include pigmentation, depigmentation, desquamation and ulceration. In moderate cases the dermatosis resembles crazy paving. A severe case may resemble an extensive burn. The legs, buttocks and perineum are most frequently involved, but any region may be affected. This is in contrast to pellagra (p. 158) in which the dermatosis occurs mainly on the exposed surfaces. The skin lesions are determined in part by associated vitamin deficiencies and in part by infections and trauma.

Mucous Membranes. Angular stomatitis, cheilosis and a smooth tongue are commonly seen, as is ulceration around the anus.

Liver. This may be enlarged and extend down to the umbilicus but the liver can be fatty without being clinically remarkable. Hepatosplenomegaly from malaria and other causes is common in the tropics.

Gastrointestinal System. Anorexia and sometimes vomiting occur; there is usually diarrhoea, with the passage of stools containing undigested food. This feature may be secondary to failure of the pancreas to secrete digestive enzymes, to intestinal mucosal atrophy or to an associated gastroenteritis.

Anaemia. Some degree of anaemia is frequently present. It oftens becomes worse during treatment. The degree of anaemia and its nature are largely determined by associated infections and other dietary deficiencies (p. 165).

Differential Diagnosis. A variety of diseases may be confused with kwashiorkor. Chronic dysentery, abdominal tuberculosis, coeliac disease, infantile pellagra and beriberi, fibrocystic disease of the pancreas and nephritis are diseases which have clinical features in common with kwashiorkor. Hookworm infection with anaemia and oedema may resemble kwashiorkor in many respects. The age of onset, the dietary and social history, characteristic skin and hair lesions, normal urine and the response to protein therapy should help to distinguish kwashiorkor.

Prevention. Ignorance and poverty are two main factors responsible for kwashiorkor. Every effort should be made to alleviate these causes. Education in nutrition, the introduction of improved farming methods and the development of food industries whereby protective foods may be made available at a reasonable cost to the consumer, are all important. In each country careful thought must be given to the provision of protein-rich foods made from local crops which are suitable both for infant feeding and for supplementing diets low in protein. Cameron and Hofvander (p. 183) give over a hundred recommended weaning recipes from many developing countries.

Even small amounts of food of animal origin, such as dried milk, egg, a little meat or concentrates of fish protein, are of great value when mixed with high protein vegetable foods. Although milk powder is a convenient source of protein it is only essential for treating established kwashiorkor. The disease can, and often has to be prevented by appropriate combinations of local foods, e.g. cereals and legumes or groundnuts.

Education of parents, particularly mothers, in regard to the value of foods and best methods of preparing them, especially at the time of weaning, is invaluable. Much is being done to alleviate this disorder by the establishment or extension of Child Welfare Clinics and Health Centres where free or subsidised skimmed milk powder or a protein food mixture is supplied, advice on diet given, and where diseases liable to lead to kwashiorkor are prevented or treated. At the same time and place the advantages to mother and child of wider spacing of births should be carefully explained and contraceptive measures provided.

Treatment. GENERAL MEASURES. An easily digested diet which provides sufficient calories and adequate amounts of protein of good biological value, together with sufficient minerals and vitamins, is essential. Dried skimmed milk is of particular value as a source of first-class protein and should be used in treating serious cases in the early stages. Calcium caseinate is also of value for this purpose but is more expensive. If neither of these preparations is available or the cost of maintaining the supply of milk becomes prohibitive, a protein-rich mixture such as 'Incaparina' should be used.

Severely ill children may be unable to maintain their body temperature even in the tropics, especially where there is a large fall of atmospheric temperature at night. Heated rooms or electric blankets are essential for such cases. Vitamins A and D, B Complex and C and therapeutic doses of iron should be given. If dermatosis is severe the skin should be cleaned and carefully protected. The child's weight tends to fall during the first days of treatment due to loss of oedema fluid. The initiation of cure is indicated by increasing appetite, improvement in general condition, loss of oedema and rise of serum albumin.

DIETS FOR SEVERE CASES. All the major units with research experience of kwashiorkor have evolved somewhat different therapeutic diets, depending on local availability of and preferences for weaning foods. The principle of all the regimes is to work up to protein intakes of 3 to 4 g/kg/day and energy intakes of 150 kcal/kg/day or more. For the first day or two, if the child is unable to feed from a spoon, a polythene tube passed through the nose into the stomach will be necessary. The following recipe for a baby food based on skimmed milk powder has been widely used in Jamaica.

Ingredients: 60 g (2 oz) skimmed milk powder
15 g (1½ teaspoons) butter
20 g (2 teaspoons) flour
250 ml (½ pint) water.

250 ml (½ pint) of this mixture contains about 22 g protein and 250 kcal.

This recipe was constructed after it had been demonstrated that skimmed milk powder alone is unable to meet a child's needs for growth and in excessive amounts is liable to cause diarrhoea. It must therefore be used only as a supplement. The mixture should be given in divided doses four to six times a day so as to provide the patient with up to 5 g of protein for each kilogram of the ideal weight of a child of the same age. On the second or third day it should be possible to start on a banana/milk or cereal/milk diet.

The following recipe is widely used in Uganda: Mash 400 g of peeled sweet bananas and mix thoroughly with 200 g of skimmed milk powder in 500 ml of water which has been brought to the boil and allowed to cool. Divide the mixture, which represents one day's ration, into six equal parts. Feed with a spoon. This diet, which provides in one day's ration about 75 g of protein and 1,200 kcal, will lead to an improvement in appetite, digestion and strength.

Where bananas are not available, as is the case in many countries where kwashiorkor is endemic, a flour made from semolina, rice, cassava, cereals, Bengal gram or other pulses will have to be used. In this case it is strongly recommended that an ounce of butter or an edible oil such as sunflower seed oil should be added as it makes the mixing of the flour and milk powder easier and the mixture is more palatable and digestible and of higher caloric value.

Anorexia may be serious, but often can be overcome by feeding the child very slowly in the mother's lap and by giving frequent feeds. Food may be taken better cold than hot. If the diarrhoea appears to be made worse on feeds containing skimmed milk, lactose intolerance may be present, in which the intestinal mucosa contains no lactase so that lactose cannot be digested into its absorbable monosaccharides, glucose and galactose. Such a child should respond to a mixture such as Casilan, cream, glucose and cereal.

As the clinical condition improves the food should be increased gradually. Whole milk powder can be substituted for skimmed; eggs, fish and bean flour can be added to the diet until the child is eating a satisfactory diet of local pattern, including adequate amounts of easily digested protein-rich foods.

Infants may lose 1-4 g of potassium chloride (13-52 mEq) in the stools in one day if there is severe diarrhoea. The effect of the resulting potassium depletion on the myocardium may cause sudden death. Potassium should be given by mouth as a routine to all infants admitted with kwashiorkor. Depending on the age and weight of the child and the severity of the diarrhoea, the dose should be from 0·5 to 1 g of potassium chloride dissolved in water and added to three or four feeds each day. There is little or no danger of potassium intoxication when the mixture is given by mouth in these doses. Some centres give magnesium as well (1-2 mEq/kg/day).

PARENTERAL THERAPY. For very ill patients in a well-equipped and well-staffed hospital, who are suffering from marked dehydration, hypoglycaemia, acid-base disturbances and electrolyte imbalance, parenteral therapy with solutions such as half isotonic Darrow's solution with 2·5 per cent dextrose may be a life-saving measure which should be started prior to the beginning of dietetic treatment. Likewise, for severe anaemia from any cause, small slow transfusions of packed erythrocytes are of the greatest value. In developing countries facilities for these measures are not available for the majority of severe cases of PCM.

VITAMINS. Vitamin A deficiency with xerophthalmia and keratomalacia (p. 134) occurs in from 1 to 70 per cent of severe cases of PCM. This is a major cause of preventable blindness in developing countries. All kwashiorkor patients should receive moderate amounts of vitamin A routinely, e.g. in a fish liver oil concentrate or multivitamin syrup, and if xerophthalmia is suspected 30 mg should be given for three days.

Biochemical signs of thiamin and niacin deficiencies are commonly associated with kwashiorkor in countries where rice or maize respectively are the staple weaning foods. Folate deficiency is also fairly frequent. It would therefore be wise to give B vitamins routinely. Children with PCM have often been indoors out of the sun for weeks and a minority of cases have associated rickets (p. 137). Vitamin K_1 in a single intramuscular dose of 10 mg should be given if there is any purpura or bleeding or if a surgical procedure is required. Therapeutic diets for kwashiorkor tend to be low in vitamin C. There is no satisfactory evidence that vitamin B_{12} has any beneficial effect on the disease, except sometimes when megaloblastic anaemia is present.

INFECTIONS AND COMPLICATIONS. These must be treated with an appropriate antibiotic or other drug depending on the nature and site of the infection. The usual signs of infection like pyrexia may not appear. Because infections are so common some authorities give penicillin and a sulphonamide routinely to all patients. Many of these children harbour worms. However, all anthelmintics are potentially toxic and must be used with due care in patients who are seriously ill. If anaemia from hookworm is so severe as to endanger life, small transfusions with packed cells should be given and will probably restore the child's condition sufficiently to permit appropriate treatment later. Iron-deficiency anaemia, which is frequently present due to dietary deficiency of protein and iron and as a consequence of infections, requires appropriate treatment (p. 725). Less commonly a megaloblastic anaemia is present which responds excellently to folic acid (p. 731). Antimalarial drugs in both prophylactic and therapeutic doses are well tolerated. The possibility of tuberculosis should always be considered, particularly if the child does not make the expected progress to recovery. If not too far advanced, it responds well to specific therapy (pp. 366-371).

CONVALESCENCE. When a child who has had severe kwashiorkor comes to be discharged from hospital he is still usually well below normal weight and height for his age. At this stage 'catch-up' (supernormal) growth is possible and obviously desirable, but it will not occur unless the child is in a favourable environment and getting all the food he will eat. If home conditions are difficult some simple convalescent home would be ideal where available. In any case follow up should be arranged to ascertain that the child does not deteriorate.

MILD KWASHIORKOR AND FOLLOW-UP CASES. Such cases can be treated as out-patients and milk in any form can be recommended, but preferably dried skimmed milk sprinkled over the food, rather than reconstituted with water with the resulting liability to infection in hot climates where facilities for sterilisation are poor. It is essential that the mothers of such patients should be given instruction in regard to hygiene, cooking and methods of feeding. The doctor should enquire about socio-economic problems and try to arrange help where possible.

Prognosis. Severe kwashiorkor has a mortality of around 20 per cent even in a well equipped hospital. Most deaths occur in the first week or 10 days. Jaundice, petechiae and stupor are bad prognostic signs. The usual causes of death are intercurrent infections and severe malnutrition, including potassium deficiency. The availability of medical care is another factor influencing prognosis.

In the long term, follow-up studies have shown that the fatty liver of acute kwashiorkor does not progress to cirrhosis. Physical growth of the brain is retarded in children whc suffer from severe PCM in the first year or two of life. There is circumstantial evidence that intelligence may be impaired, particularly if the child goes home to an environment in which catch-up growth cannot occur. Hence the great importance of trying to arrange the best possible conditions for the child's nutrition and mental development after leaving hospital.

Nutritional Marasmus

The importance of nutritional marasmus as a cause of mortality and morbidity in infants is still not fully appreciated. In parts of some developing countries marasmus is of greater clinical importance than kwashiorkor. It affects principally infants under 1 year of age in contrast to kwashiorkor which is chiefly encountered in children between 1 and 4 years of age. Marasmus is more likely to occur in poor people in underdeveloped countries who live in cities, while kwashiorkor occurs more frequently in those living in rural areas. The factors which predispose to marasmus are a rapid succession of pregnancies, and early and often abrupt weaning, followed by dirty artificial feeding of the infants with very dilute milk or milk products given in inadequate amounts to avoid expense. Thus the diet is low in both calories and protein. In addition unsatisfactory home conditions make the preparation of uncontaminated feeds almost impossible. Repeated infections therefore develop, especially of the gastrointestinal tract, which the mother often treats by starvation, the infant receiving water, rice water or some other non-nutritious fluid (Fig. 18, p. 124).

The most important cause of marasmus, early weaning, is in contrast to the late weaning, often extending over two years, which is characteristic of kwashiorkor. The mother may be induced to stop breast feeding for various reasons, including the presence of infections in herself or in the infant. She may have been influenced unwisely by advertisements which advocate the advantages of artificial food products. One reason for stopping breast feeding is economic pressure on the mother to go out and work. A second is the beginning of another pregnancy. There is widespread belief among uneducated women in developing countries that the milk of a pregnant woman is bad for her child.

Clinical Features. The two constant features of marasmus are: (1) retardation of growth and reduction of weight which is much more marked than that of length, and (2) wasting of muscles and subcutaneous fat which gives the infant a wizened, old appearance. There is usually watery diarrhoea or semi-solid, bulky, acid stools. In contrast to kwashiorkor, oedema is absent and the characteristic changes in the hair and skin, apathy and anorexia are seldom encountered. A careful search must be made for chronic infection like tuberculosis which predisposes to marasmus. The features of associated vitamin disorders such as angular stomatitis or keratomalacia, may develop, as may a deficiency of minerals, especially potassium and magnesium. Dehydration frequently occurs as a consequence of gastro-intestinal infection.

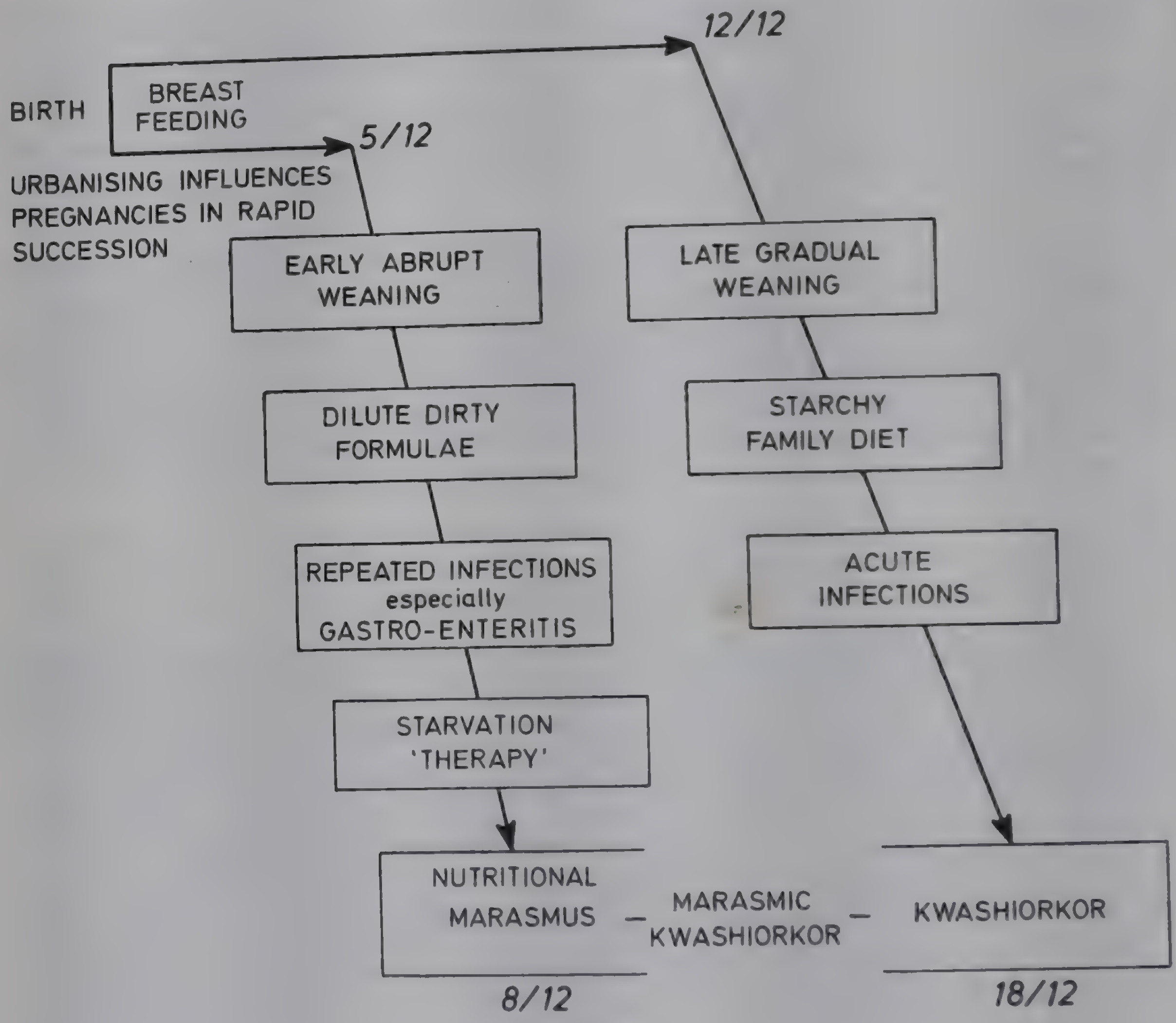


FIG. 18

Paths leading from early weaning to nutritional marasmus and from protracted breast feeding to kwashiorkor.

(By courtesy of Dr D. S. McLaren and the editor of the *Lancet*.)

Treatment and Prevention. In the acute stage of marasmus survival depends primarily on the efficiency with which measures can be applied to combat dehydration and restore electrolyte balance. In addition the child must be given a satisfactory diet along similar lines to those described for kwashiorkor on pages 120 and 121 and a supplement of vitamins. Even when these objectives have been successfully accomplished the death rate may be higher and the morbidity greater than in severe cases of kwashiorkor.

Prevention is a complex and difficult problem. Education of mothers so that they will continue breast feeding for as long as possible is of the greatest importance. Further research is urgently needed into improved methods of feeding both healthy and ill infants in developing countries. The epidemiology of the failure of lactation and the control of infection in infants are other important matters requiring further investigation. It is probable that in the future marasmus will become of increasing clinical importance in developing countries as a consequence of a continuing decline in breast feeding and the urbanisation of uneducated families, socially insecure and living in poor, insanitary houses and with insufficient money to buy adequate supplements of milk or milk substitutes.

Nutritional Dwarfing

Some children adapt to very prolonged mild to moderate calorie and/or protein deficiency by a proportional failure of growth. They are light in weight and short in stature but have superficially normal body proportions and subcutaneous fat. Such children are more prone to infections than normal. Unless the weight for age of such a child is checked against normal standards (Table 17, p. 1006) it is easy for the doctor in a busy clinic to miss this form of PCM.

Mild to Moderate PCM (The Underweight Child)

For every florid case of kwashiorkor or marasmus there are several children in the community with mild to moderate PCM. The situation is like an iceberg. There is more malnutrition below the surface than is recognisable on clinical inspection. The children with subclinical PCM can however be detected by their weight for age, which is less than 80 per cent of the international standard (Table 18). In areas where kwashiorkor is the predominant florid form of PCM, subclinical cases have reduced serum albumin and sometimes other biochemical signs of protein deficiency ('pre-kwashiorkor'). In parts of many developing countries surveys may show up to 5 per cent of children under 5 years with signs and symptoms of kwashiorkor or marasmus while 50 per cent are underweight.

The great importance of mild to moderate PCM is that these children are growing up smaller than their potential and they are very susceptible to gastroenteritis and respiratory infections, which in turn can precipitate frank malnutrition. Mild to moderate PCM is probably the major underlying reason why the 1 to 4 year mortality in a developing country can be 30 to 40 times higher than in Europe or North America. Official statistics record most of these deaths as due simply to infections.

WATER AND ELECTROLYTES

The normal concentrations of ions, both in the intracellular and extracellular fluids, is preserved by a balance between intake of water and electrolytes in the diet and the output in the excretions.

Water. The water intake comprises the fluid drunk and the water in the food eaten. The metabolic water formed by the oxidation of carbohydrate, protein and fat is also available. The output consists of the urine, the water in the faeces and the water evaporated from the skin and lungs.

The water and other fluids drunk are approximately equal to the urine output. It is this fact that makes the 'fluid balance chart' (kept by the nursing staff) a useful procedure. It is particularly valuable in the care of febrile patients in the tropics, who are liable to become dehydrated unless carefully supervised.

Salt. It is certainly true that life can proceed without the deliberate addition of sodium chloride to food; yet for civilised man salt appears to be an indispensable adjunct to life. Most healthy adults take from 1½ to 2½ litres of fluid and 5 to 20 g NaCl (70 to 350 mEq Na) daily.

In tropical countries the intake of water and salt has to be increased to make up for their loss in sweat. Most people suffering from cardiac failure and some with hypertension benefit if the salt in their diet is restricted. A few remote communities who do not have access to salt appear to be free of essential hypertension.

The normal distribution of water and electrolytes in the body and the disturbances which result when their intake or output is diminished or increased are discussed in detail on pages 185 to 197.

MINERALS

The following physiologically important elements occur in the human body: sodium, chlorine, calcium, sulphur, iron, iodine, fluorine, zinc (phosphorus, potassium, magnesium, copper, cobalt, chromium and manganese). Deficiencies of those bracketed are not known to occur in man *solely* as the result of an inadequate dietary intake.

Elements of Importance in Human Dietetics

Calcium

The body of an adult normally contains about 1,200 g of calcium. At least 99 per cent of this amount is present in the skeleton, where calcium salts (chiefly hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$) held in a cellular matrix provide the hard structure of the bones and teeth. Obviously all of this calcium comes from the diet. Among common foods, the calcium-containing protein of milk (caseinogen) is much the richest source, which is one reason why milk and cheese are especially valuable for growing children. Half a litre (just under a pint) of cow's milk contains about 0·6 g of calcium. Most other foods contribute much smaller amounts. However, peas, beans, other vegetables and particularly cereal grains are frequently the chief contributors because of the large amounts eaten.

Drinking water can provide significant amounts of calcium. In Britain the average intake from this source is about 75 mg Ca/day; but the variations are large: from none in water from peaty, acidic hill lochs in Scotland to 200 mg or even more in water obtained from wells sunk in chalk or limestone.

ABSORPTION. The problem of calcium absorption is extremely complicated. It is not known why 70 to 80 per cent of the calcium in the food is normally excreted in the faeces. Calcium absorption may be impaired either by lack of vitamin D, by any conditions causing small intestinal hurry, e.g. diarrhoea, by the combination of calcium with excess fatty acids to form insoluble soaps, e.g. steatorrhoea, or by certain substances in the diet which can form insoluble salts with it. These include foods rich in oxalic acid (e.g. spinach) and, of much greater importance, phytic acid. Phytic acid is present in the outer layers of cereal grains. Hence bread made from 'high extraction' flour ('wholemeal' bread) contains more phytic acid than 'white' bread. To overcome the influence of phytic acid, calcium carbonate has been added to flour in Britain.

DAILY RECOMMENDED INTAKES OF CALCIUM. The Department of Health and Social Security (UK) recommended in 1969 a daily intake of 500 mg for adult men and women, rising to 1,200 mg during pregnancy and lactation. For adolescent boys and girls the recommended intake was from 600 to 700 mg daily.

In many parts of Africa and Asia children develop healthy bones and adults remain in calcium balance despite calcium intakes which may be no more than half the above recommendations. Abundant sunshine possibly produces this effect. However a daily intake of 1,000 mg should be taken during pregnancy and lactation.

Deficiency of calcium and vitamin D go hand in hand and are best considered together (p. 134).

Phosphorus

Eighty-five per cent of the phosphorus in the normal body is present in the bones in combination with calcium. The remainder is chiefly in the cells. Phosphate is essential for most metabolic processes.

Phosphorus is present in all natural foods, though in refined and processed foods the phosphorus content may be greatly reduced. The best sources are those foods that also contain good amounts of calcium and protein. Phosphorus normally presents no problem for the dietitian. A useful working rule is 'take care of the calcium and the phosphorus will look after itself'. Dietary deficiency of phosphorus is not known to occur in man.

Iron

A good mixed diet with an average helping of meat and vegetables contains about 12-15 mg of iron. Cheap monotonous high carbohydrate diets based on refined wheat flour contain much less. Foods which are particularly rich in iron are meat, liver, eggs, wholemeal cereals, oatmeal, peas, beans and lentils. The availability of the iron varies in different foods. Tests in man with ^{59}Fe incorporated into foods have shown that iron is absorbed well from meat, haemoglobin and wine, moderately from pulses and poorly from eggs. Absorption is enhanced in iron deficient individuals. An account of the measures for the prevention and treatment of iron deficiency anaemia is given on pages 725 and 726. Next to obesity this is the most important nutritional cause of ill-health in Britain and other prosperous countries.

SIDEROSIS. Iron overload can occur in patients with chronic haemolysis or who have received multiple blood transfusions. Dietary iron overload is seen in South African Bantu men who cook and brew beer in iron pots. They may ingest as much as 100 mg of iron a day. Iron accumulates in the liver and when severe can lead to cirrhosis. A similar condition has been described in other countries following excessive indulgence in cheap wines which can contain 30 mg of iron per litre.

Iodine

Simple enlargement of the thyroid gland attributed to lack of iodine in the food and drinking water occurs particularly in mountainous regions far from the sea. Factors other than the lack of iodine in the diet contribute to the causation of simple goitre (p. 647).

SOURCES. Iodine in small amounts is widely distributed in living matter. Seafoods are the only rich source in the diet. Vegetables and milk may contain useful amounts. Fresh water usually contains only small amounts of iodine, e.g. 1-50 μg/*l* in Britain, so that it contributes little to the needs of the body. The iodine content of the water in a locality is more important as an index of the amount of iodine that is likely to be provided by the cereals and vegetables that grow in the soil which the water irrigates.

PROPHYLACTIC USES. The prophylactic requirement is around 150 μg/day. The Medical Research Council recommended the addition of potassium iodide to all table salt in Britain as this has been proved to be highly successful in reducing the incidence of simple goitre in Switzerland, the USA and other parts of the world. Regrettably the legislation required to enforce this recommendation in Britain has not yet been enacted.

Fluorine

Fluorine has recently been shown to be an indispensable nutrient for rats. Its regular presence in minute amounts in human bones and teeth and its influence on the prevention of dental caries justifies its inclusion as an element of importance in human dietetics.

SOURCES. Most adults ingest between 1 and 3 mg of fluorine daily. The chief source is usually drinking water, which, if it contains 1 part per million (p.p.m.)

of fluorine, will supply 1-2 mg day. Soft waters usually contain no fluorine, whilst very hard waters may contain over 10 p.p.m. Compared with this source, the fluorine in foodstuffs is of little importance. Very few contain more than 1 p.p.m.: the exception is sea-fish which may contain 5-10 p.p.m. Another significant source is tea. In Britain and Australia, where people drink tea frequently, the adult intake from this source may be as much as 1 mg daily.

USE OF FLUORIDE IN THE PREVENTION OF DENTAL CARIES. Epidemiological studies in many parts of the world have established that where the natural water supply contains fluoride in amounts of 1 p.p.m. or more, the incidence of dental caries is lower than in comparable areas where the water contains only traces of the element.

Fluorides become deposited in the enamel surface of the developing teeth of children. Such teeth are unusually resistant to caries for reasons not yet fully understood; it may be that traces of fluoride in the enamel discourage the growth of acid-forming bacteria. Alternatively, the calcium hydroxyapatite of the enamel may be rendered more resistant to organic acids by combination with traces of the element. It should be noted that fluoride is not deposited in fully developed adult teeth, so that no benefit to adults can be expected when they begin for the first time to drink water containing traces of fluoride.

The deliberate addition of traces of fluoride to those public water supplies which are deficient is now a widespread practice throughout North America where at least 90 million people are now drinking fluoridated water. In at least seventeen other countries similar projects have been started.

In view of the widespread incidence of caries throughout Britain, the case for the addition of fluoride up to 1 p.p.m. to the water supplies of those areas where it is lacking has been strongly supported by carefully controlled trials. The announcement by the Government in 1956 that action may be taken to implement fluoridation of water was very welcome. Regrettably, many local authorities are not yet adding fluoride to their water supplies.

FLUOROSIS IN MAN. In parts of the world where the water fluoride is high (over 3 to 5 p.p.m.) mottling of the teeth is common. The enamel loses its lustre and becomes rough. Bands of brown pigmentation separate patches as white as chalk. Small pits may be present on the surface. Mottling is usually best seen on the incisors of the upper jaw. The effect is purely cosmetic; fluorotic teeth are resistant to caries and not usually associated with any evidence of skeleton fluorosis, or with any impairment of health.

CHRONIC FLUORINE POISONING. This occurs in several localities in India, China, Argentina, East and South Africa, where the water supply contains over 10 p.p.m. fluoride. Fluorine poisoning has also occurred as an industrial hazard among workers handling fluorine-containing minerals such as cryolite, used in smelting aluminium. The main clinical features are referable to the skeleton which shows sclerosis of bone, especially of the spine, pelvis and limbs, and calcification of ligaments and tendinous insertions of muscles.

Sulphur

This is mainly supplied by the S-containing amino acids in the diet—methionine and cysteine; effects of its deficiency are therefore inseparable from those of protein.

Zinc

A syndrome has recently been described in Egypt and Iran of dwarfism and hypogonadism in late teenage boys. Serum zinc was low and prolonged treatment with zinc sulphate (27 mg Zn per day) was accompanied by accelerated growth and sexual maturation. The cause is thought to be interference with zinc absorption by phytate in unleavened bread, which is the staple diet.

Other minerals

For further information see sodium (p. 186), potassium (p. 189), copper (p. 715), cobalt (p. 165) and magnesium (p. 193).

THE VITAMINS

Although vitamin deficiency disorders are now uncommon in Britain they deserve consideration in detail because they are still widespread in many parts of the world. Even in industrial countries certain types of people are known to have chances of developing some vitamin deficiency. Doctors should be ready to diagnose these treatable conditions in their early stages.

Definition. Vitamins are organic substances which the body requires in small amounts for its normal metabolism and yet cannot synthesise for itself in adequate quantities. A large number of substances conforming to this definition have been recognised by feeding tests on animals, but deficiencies of only 10 vitamins have, so far, been demonstrated to have clinical effects in man. These 10 are:

Fat-soluble

- Vitamin A
- Vitamin D
- Vitamin K

Water-soluble

- Vitamin C—Ascorbic acid
- Vitamin B complex
  - Thiamin
  - Niacin
  - Riboflavin
  - Pyridoxine
  - Cobalamins (B_{12})
  - Folate

Vitamin E is another vitamin present in human tissues, yet not proved essential for human needs. It has the interesting property of reducing tissue oxidation and has been recommended for therapeutic use in many human diseases, mostly quite unconnected with dietary deficiencies. So far, however, it has no proven therapeutic value.

Factors influencing the Utilisation of Vitamins

1. **Availability.** Not all of a vitamin may be in absorbable form. For instance niacin in maize is bound in such a way that it is not absorbed from the gut. Fat-soluble vitamins may be deficient if dietary fat is not eaten or absorbed.

2. **Antivitamins.** These are known to be present in some natural foods, e.g. thiaminase in raw fish. Some synthetic antagonists of the vitamins are used as drugs in the therapy of neoplasms (e.g. methotrexate, p. 749) or of infections (e.g. pyrimethamine, p. 968). Neoplastic cells and micro-organisms are much more sensitive than normal body cells but with high doses of the antivitamin a conditioned vitamin deficiency can occur.

3. **Provitamins.** Substances occur in foods which are not themselves vitamins but are capable of conversion into vitamins in the course of digestion. Thus the carotenes are the provitamin of vitamin A and, to some extent at least, the amino acid tryptophan can be converted to niacin.

4. **Biosynthesis in the Gut.** The normal bacterial flora of the gut is capable of synthesising significant amounts of certain vitamins (e.g. vitamin K). Bacteria are also capable of extracting vitamins from the ingested food and retaining them until excreted in the faeces. Except for vitamin K, bacteria are more likely to reduce than to increase the amounts of vitamins available for absorption, as is demonstrated in the blind loop syndrome (p. 494).

5. **Biosynthesis in the Skin.** Vitamin D need not be provided in the diet provided the skin is regularly exposed to adequate sunshine (p. 137).

These considerations indicate how difficult it may be in practice to define the nutritive value of a diet simply from chemical analysis of its vitamin content.

Recommended Intakes of Vitamins

There has been much confusion in the use of terms to define the amounts of vitamins required in the diet to maintain health, e.g. minimum requirements, optimum requirements, recommended allowances, etc. Hence the importance of the Report (1967) of a joint FAO/WHO group of nutritional experts on the requirements of vitamin A, thiamin, riboflavin and niacin. 'Recommended intake', which was chosen as the most suitable term for this purpose, was defined as 'the amount of the vitamin considered sufficient for the maintenance of health in nearly all people'. It was not expected to cover additional needs which may result from such conditions as infections, malabsorption or metabolic abnormalities. In addition the recommended intake is applicable only when the requirements for calories and other nutrients are met. The Committee stated that in view of the well-recognised roles of thiamin, riboflavin and niacin in energy expenditure, it seems reasonable to express these requirements in terms of mg/1,000 kcal. Vitamin requirements vary with factors such as body weight, physical activity, pregnancy and lactation and the presence of infections. The recommended daily intake for an adult male per 1,000 kcal ingested is 1 mg for thiamin, 1·7 mg for riboflavin and for niacin, 18 niacin equivalents (p. 158).

The Committee stated that in view of the availability of retinol as a reference standard, the practice of expressing vitamin A values in terms of international units (i.u.) is no longer desirable. Recommended intakes should be described in units of weights. The conversion factor for vitamin A is 1 i.u. = 0·3 μg of retinol. Likewise for vitamin D the conversion factor is 1 i.u. = 0·025 μg of crystalline cholecalciferol (1 μg of cholecalciferol = 40 i.u.).

The recommendations of the joint FAO/WHO Committee have received universal acceptance. Recommended intakes of nutrients for the United Kingdom were published in 1969.

VITAMIN A—RETINOL

Chemistry and Physiological Action. Retinol is found only in foods of animal origin. Animals obtain the vitamin from its precursor or provitamin—the pigment, carotene. The conversion of β carotene into retinol in the human body is not complete and involves considerable losses. It takes place largely, if not entirely in the walls of the small intestine. The absorption of both retinol and carotene is facilitated by fats and bile salts.

It seems likely that retinol has a place in the metabolism of all human cells, but the precise way that it behaves is not yet explained in biochemical terms except in the retina.

Dietary Sources. Retinol is chiefly found in milk, butter, cheese, egg yolk, liver and some of the fatty fish. The liver oils of fish are the richest natural sources but these are used as nutritional supplements rather than foods.

Carotene is widely distributed among plant foods. It is found chiefly in green vegetables in association with chlorophyll, so that the green outer leaves of vegetables like cabbage and lettuce are good sources, while the white inner leaves contain little or none. Other useful sources are yellow and red fruits and vegetables. Vegetable oils are devoid of vitamin A activity except red palm oil which is extensively produced in West Africa, Indonesia and Brazil. This oil is a rich source of carotene. In Britain and some other countries retinol is added artificially to margarine to provide the same concentration as that of good quality summer butter.

Losses in the Preparation and Handling of Food. Both retinol and carotene are stable to ordinary cooking methods, though some loss may occur at temperatures above 100° C. as when butter or palm oil is used for frying. Fruits and other foods that are dried in the sun lose much of their vitamin A potency. The stability of carotene in tinned foods was dramatically shown by Drummond who found that cooked carrots that had been sealed in air-tight containers in 1824 for the Arctic voyage of H.M.S. *Hecla* had much the same carotene content as fresh carrots when the containers were finally opened in 1939.

Recommended Intakes. Recommended daily intakes of retinol are 300 μg for infants and young children, 500-600 μg for children of 9 to 15 years, 750 μg for adolescents and adults, and 1,200 μg for lactating women. In many parts of the world most or all the requirements are obtained from carotenoids in vegetable foods. Because only approximately $\frac{1}{3}$ of β carotene is absorbed into the intestinal wall and then only $\frac{1}{2}$ of this is converted into retinol, 1 μg retinol equivalent (= 1 μg retinol) is now taken as = 6 μg β carotene. Healthy adults in Britain have large stores of 90 to 150 mg retinol in their livers.

Pathology. Deficiency of the vitamin results in morphological changes in the epithelial surfaces of all parts of the body. The cells undergo squamous metaplasia whereby they become flattened and heaped one upon another. The sebaceous glands and hair follicles of the skin and the tear glands of the eye become blocked with horny plugs of keratin so that their secretions diminish. The lack of tears and the heaping up of epithelium on the scleral conjunctiva and cornea produce the condition of *xerophthalmia*. When softening, ulceration and necrosis of the cornea develop, the condition is referred to as *keratomalacia* (p. 134).

Therapeutic Uses. A dietary deficiency of vitamin A arises only when there is an insufficient supply of dairy produce, fish and vegetables. Hence the clinical features of vitamin A deficiency are very rare in Britain and in other affluent countries. In contrast in underdeveloped countries in Asia, Africa and South America deficiency of the vitamin is common and leads to very serious consequences (see below).

Retinol is invaluable in the treatment of xerophthalmia, keratomalacia and of night blindness—when this is due to dietary failure. It should also be given to malnourished people who show evidence of follicular keratosis.

Where vitamin A deficiency is prevalent, minor disorders of the eyes and skin often recover more rapidly in children receiving regular prophylactic doses of the vitamin. There is also the clinical impression that it often improves their growth and well-being.

The prescription of retinol for the prevention of the common cold and other conditions in people taking a good mixed diet is not justified by any reliable clinical evidence.

Night Blindness

Retinol is an essential component of the pigment rhodopsin (visual purple) on which vision in dim light depends. Hence lack of retinol may result in impairment of 'dark adaptation' which can be measured by means of an adaptometer. Night blindness is common, as also is vitamin A deficiency, in poor people living in underdeveloped countries; it can occur in the malabsorption syndrome in affluent countries. In such cases it responds excellently to retinol. Fatigue and anxiety states may cause persons to complain of night blindness. It may also result from organic disease of the eye such as retinitis pigmentosa. The diagnosis of vitamin A deficiency is supported by low plasma vitamin A concentration and is confirmed by marked improvement in dark adaptation following therapeutic doses of the vitamin.

Xerosis Conjunctivae, Bitôt's Spots and Xerophthalmia

The earliest sign of xerosis conjunctivae is a dry, thickened and pigmented bulbar conjunctiva. The pigmentation gives the conjunctiva a peculiar smoky appearance. Bitôt's spots are glistening white plaques formed of desquamated thickened conjunctival epithelium, usually triangular in shape and firmly adherent to the underlying conjunctiva. Xerosis conjunctivae and Bitôt's spots are certainly common in children whose diet is deficient in vitamin A but they also occur in children whose intake of the vitamin is satisfactory. When dryness spreads to the cornea it takes on a dull, hazy, lacklustre appearance due to keratinisation, and xerophthalmia is said to be present.

In young children, xerophthalmia is almost always attributable to recent vitamin A deficiency and is usually associated with PCM. In older children and in adults its interpretation is less simple. Exposure to dust and glare may produce similar changes. They should, however, always call attention to the diet. Xerophthalmia is very important in young children because once the cornea is involved the process can rapidly progress to keratomalacia.

Keratomalacia

This disease causes blindness among Indians, Indonesians and other rice-eating people of Asia; it also occurs in parts of Africa, the Middle East and Latin America. In Europe and North America it is very rare. Children between the ages of 1 and 5 years are most commonly affected. It only occurs in persons who have been living for long periods on diets almost entirely devoid of vitamin A.

The disease is frequently associated with PCM.

The earliest manifestations are night blindness and xerophthalmia. Later the cornea undergoes necrosis and ulceration. Unless early and adequate treatment is given, there is a grave risk of blindness or death from associated diseases. In many Eastern countries keratomalacia is at least as important as smallpox and gonorrhoea in destroying the sight of children.

Treatment. A good all round diet and attention to any associated infection is essential for the treatment of the above disorders. In xerophthalmia or severe adult cases of night blindness the administration of vitamin A in a dose of 30 mg retinol (100,000 i.u.) daily for three days should be started immediately. It is recommended that half the dose should be given orally in the form of halibut or similar rich fish oil and half intramuscularly as retinol acetate or palmitate, in order to ensure that the patient is actually getting the vitamin. The practice of instilling cod-liver oil directly into the eye is not recommended. During convalescence 9 mg of retinol in the form of a fish-liver oil orally is adequate.

For the prevention and treatment of secondary bacterial infection, antibiotics are of great value. Local treatment of the eye will be required only if disorganisation is already present, in which case the services of an ophthalmic surgeon should be obtained.

Prevention. The essential needs for prevention are the education of mothers, better maternal and child health services and an improvement in food production. The prime objective is to make sure that infants and young children obtain adequate amounts of vitamin A or carotene in their diet or as a supplement. In countries where vitamin A deficiency is endemic the distribution of a national concentrated source of vitamin A is desirable, especially for children. For this purpose cod-liver, shark-liver or red palm oil can usefully be given according to which is most easily available locally. Prophylactic doses of retinol for infants, children and adults are given on page 133.

BLINDNESS. It has been estimated that there are more than 10 million blind people in the world and that most of these become blind before the age of 5 years. The situation is all the more tragic because probably about two-thirds of the cases of blindness are preventable if energetic Public Health measures were introduced and good ophthalmic clinics were available in adequate numbers. Vitamin A deficiency is one of the eight most common causes of blindness, the others being trachoma, smallpox, onchocerciasis, gonococcal ophthalmia, accidents, cataract and glaucoma.

Follicular Keratosis (Phrynoderma, 'Toad Skin')

In this condition the hair follicles are blocked with horny plugs of keratin, rendering the skin surface rough and dry. The typical distribution is over the backs of the upper arms and the fronts of the thighs. Therapeutic trials in Africa have repeatedly shown a striking clinical improvement in follicular keratosis when patients are given halibut liver oil or red palm oil. Nevertheless, it is not a specific sign of vitamin A deficiency, since it occurs not uncommonly in people who, by every other criterion, are adequately nourished in respect of vitamin A. It differs in appearance from the folliculosis of scurvy (p. 149).

VITAMIN D

Chemistry. A number of distinct but closely related compounds possess rickets-preventing (antirachitic) properties. These are all sterols, chemically related to cholesterol and to the hormones of the adrenal cortex and sex glands. Certain of these on exposure to ultraviolet irradiation undergo a small structural change which makes them antirachitic. Only two 'activated' sterols are of importance in nutrition and therapeutics. These were first described as vitamins D_2 and D_3 and are still commonly referred to as such. (The material originally described as vitamin D_1 was subsequently shown to be an impure mixture of sterols.)

Vitamin D_2 (ergocalciferol) is manufactured by the action of ultraviolet light on ergosterol, a sterol found in fungi and yeasts. When the term 'calciferol' is used in clinical practice it refers to ergocalciferol. Although widely used in therapeutics, it occurs very rarely in nature. *Vitamin* D_3 (*cholecalciferol*) is the natural form of the vitamin which occurs in man and other animals. Its presence in very high concentrations in fish-liver oils is made use of in therapeutics.

Metabolism and Mode of Action. We obtain some of our vitamin D preformed by eating fish or dairy foods. Ingested vitamin D requires bile and probably fatty acids for its absorption from the gut. In most people it is probable that a larger portion of the vitamin D supply is normally formed by ultraviolet irradiation of 7-dehydrocholesterol in the skin. The ultraviolet light comes from the sun and the amount of exposure is the limiting factor in this synthesis of cholecalciferol in the skin. It has been estimated that exposure of the face of a European infant to sunshine for a few hours a week produces sufficient vitamin D to prevent rickets. It has been suggested that the pigment in the skin of coloured people living in the Tropics protects them from the liability to vitamin D intoxication. On the other hand their skin pigment may make them more susceptible to rickets and osteomalacia when they emigrate to higher latitudes where the intensity of sunlight and people's exposure to it are relatively small.

Cholecalciferol, whether ingested or formed in the skin, enters the blood stream. Unlike vitamin A, stores of vitamin D in the body are not large: only a little is stored in the liver and moderate amounts in adipose tissue. Recent work has shown that cholecalciferol is not the active form of the vitamin. It is converted in the liver to 25-hydroxycholecalciferol. This is carried to the kidney, where it is further hydroxylated to 1,25-dihydroxycholecalciferol. The dihydroxy metabolite is several times more potent than cholecalciferol itself. It stimulates the synthesis in the small intestinal epithelial cells of a specific calcium transport protein, which facilitates calcium absorption and hence ensures an adequate concentration of mineral at the growing and active sites of the bones. Here calcium comes in contact with inorganic phosphates, liberated from organic phosphates under the influence of phosphatase produced by the osteoblasts. The calcium phosphate thus formed is then used to calcify new bone. It is possible that vitamin D has an additional direct stimulating action on bone but the mechanism underlying this is uncertain. In states of vitamin D deficiency the characteristic change in the bones is a reduced calcium phosphate content, particularly at the actively growing points.

Dietary Sources. The sources of the natural vitamin are all fat-containing animal products. The richest sources are fatty fish and their liver oils, some of which contain thousands of micrograms of vitamin D per 100 g edible portion. Vitamin D is also present in vitaminised margarine (p. 144) and in much smaller quantities in dairy products such as butter and eggs. It is important to remember that milk has a very small content of vitamin D, namely 0·125 μg (5 i.u.) per 100 g. Cereals, vegetables and fruit contain no vitamin D and meat and white fish insignificant amounts.

In many parts of the world children and adults eat little or no vitamin D in their diet yet they show no signs of vitamin D deficiency provided their skin is exposed regularly to ultraviolet light rays from the sun. For this reason a very low dietary intake of vitamin D may not have great significance unless an individual is always indoors, heavily clothed or living in a temperate latitude city where direct sunlight is weak and infrequent.

Recommended Intakes. The recommended daily dietary intake for infants and children up to 5 years of age and for pregnant or lactating women is 10 μg. For older children and adults about 2·5 μg is adequate.

Rickets

Rickets is a disease of calcium and phosphorus metabolism which occurs when infants or children obtain insufficient vitamin D. In addition, the intake of calcium is usually low because of insufficient milk in the diet.

Rickets is still an important clinical problem in some developing countries, especially in large towns and cities. In such countries infants in their first year are mainly affected due to an inadequate intake of vitamin D because of the low content of this vitamin in both human and animal milk and the failure to provide them with a supplement of vitamin D in any form. In addition, for various social and cultural reasons, their mothers wrap them up in clothes which prevents their exposure to sunlight. Lack of exposure to ultraviolet light in slums and old walled cities, particularly if the mothers are living in purdah, is another cause of vitamin D deficiency. By the second year the infant is able to crawl about in the sunshine and spontaneous healing usually occurs. In contrast the age-group mainly affected in Britain and other affluent countries is from 1 to 3 years and sometimes older, and the disease is now rare. This is the result of a variety of measures which have led to greatly improved standards of nutrition and housing. Of particular importance are the various schemes which have resulted in a satisfactory supply of milk, the distribution of cod-liver oil and other sources of vitamin D and the fortification with vitamin D of preparations of dried milk, margarine and some proprietary cereal foods. That it would be rash to suggest that any of these measures is now redundant is clearly indicated by reports of limited outbreaks of clinical rickets in coloured immigrant children in Glasgow, London and Birmingham and occasionally in underprivileged and neglected white children living in other cities. Rickets has been characteristically a disease of the poor rather than the rich. Milk (providing calcium) and cream, butter and eggs providing a satisfactory dietary source of vitamin D may be too expensive for poor urban families. If the diet of such families consists predominantly of cereals the inhibitory effect of phytic acid in the cereals on the absorption of calcium may be rachitogenic. A plentiful supply of cereals provides calories which may enable growth to take place faster than the skeleton can be properly formed if calcium absorption is inadequate. The disease is also liable to occur in premature babies who grow rapidly.

Chemical Pathology. With the deficiency of calcium in the body, the calcium in the blood serum tends to fall from its normal level of about 5 mEq/*l* (10 mg/100 ml) of which approximately 50 per cent is available in the ionised form. It may fall as low as 2·5 mEq or even less, which usually causes tetany (p. 652). More commonly the serum phosphate (as phosphorus) falls from the normal value of phosphorus of 4 mg/100 ml in childhood to 3 mg or less. This is thought to be due to the activity of the parathyroid glands which respond to a slight reduction in serum calcium by increasing the excretion of phosphorus in the urine.

Clinical rickets may occur when the levels of calcium and phosphorus in the serum are still within normal limits. A diagnostic change is an increase in serum alkaline phosphatase. This enzyme is formed by the osteoblasts which accumulate in the osteoid tissue at the growing points of the bones. These cells, unable to make bone without a sufficient supply of calcium, probably liberate into the circulation the excess of this enzyme which they cannot use.

Clinical Features. The infant with rickets has often received sufficient calories and may appear well nourished, but he is restless, fretful and pale, with flabby and toneless muscles. Excessive sweating of the head is common. The abdomen is distended as a result of the flabby abdominal muscles, the atony of the intestinal musculature and the intestinal fermentation that may arise from excessive carbohydrates in the diet. Gastrointestinal upsets with diarrhoea are common. The infant is prone to respiratory infections. Development is delayed so that the teeth often erupt late and there is failure to sit up, stand, crawl and walk at the normal ages.

The bony changes are the most characteristic and easily identifiable signs of rickets. There is extension and widening of the epiphyses at the growing points, where cartilage meets bone. The earliest bony lesion is often craniotabes—small round unossified areas in the membranous bones of the skull, yielding to the pressure of the finger, with a crackling feeling, like parchment. This sign is of particular value in the diagnosis of rickets in developing countries where the disease is common in infants under 1 year of age. It usually disappears within 12 months of birth. It is rarely seen in Britain where the disease usually develops in children between 1 and 3 years of age. Two other early signs are enlargement of the epiphyses at the lower end of the radius and at the costochondral junctions of the ribs, the latter known as the 'rickety rosary'. Later there may be 'bossing' of the frontal and parietal bones and delayed closure of the anterior fontanelle. Later still, there may be deformities of the chest such as undue prominence of the sternum ('pigeon chest') and 'Harrison's sulcus'—the latter apparently caused by the indrawing of the softened ribs on inspiration during whooping-cough or other respiratory infections to which rachitic children are prone.

If rickets continues into the second or third year of life, these signs may persist or be magnified. Deformities such as kyphosis develop as a result of the new gravitational and muscular strains, caused by sitting up and crawling. At the same time there may be enlargement of the lower ends of the femur, tibia and fibula. When the rachitic child begins to walk, deformities of the shafts of the leg bones develop, so that 'knock knees' or 'bow legs' are added to the clinical picture. The kyphosis is often replaced by lordosis. Pelvic deformities may follow and lead later to serious difficulties at childbirth in women who have suffered from rickets in childhood.

When there is a reduction in the level of ionised serum calcium infantile tetany may result, with spasm of the hands and feet and of the vocal cords.

The latter causes a high-pitched, distressing cry and great difficulty in breathing. In bygone days—when florid rickets was common—tetany was sometimes associated with alarming general convulsions.

Diagnosis. In countries where the disease is now rare, there is an increasing likelihood that mild cases will be missed. A flabby baby towards the end of its first year, unable to pull itself up, with too few teeth showing and liable to profuse sweats, should always be suspected of rickets. The diagnosis may be supported by the dietary history. Early evidence of rickets may be overlooked in a child ill with bronchopneumonia or diarrhoea. If there is any doubt or suspicion, radiological examination of the wrist will show characteristic changes at the epiphyses; the outline of the joint is blurred and hazy, and the epiphyseal line becomes broadened. Later, in older children, the classical concave 'saucer' deformity is shown. A raised level of serum alkaline phosphatase should give further support to the diagnosis. However, the alkaline phosphatase may be unchanged when rickets and PCM occur together and, on the other hand, occasional normal children with no dietary or clinical evidence of rickets may have enzyme levels above the expected range.

It is sometimes necessary to distinguish rickets from other rare disorders involving the bones, such as infantile scurvy, congenital syphilis, achondroplasia and osteogenesis imperfecta. Radiological examination of the bones is helpful in differentiating these disorders.

Treatment. The two essentials of treatment are the provision of a supplement of vitamin D and an ample intake of calcium.

VITAMIN D PREPARATIONS. A therapeutic dose of vitamin D varies from 25 to 125 μg (1,000-5,000 i.u.) daily, depending on the severity of the disease and the age of the child. In contrast, the prophylactic dose is 10 μg or less daily depending on the intake of vitamin D from other sources. The B.P. preparation of cod-liver oil contains approximately 10 μg per 5 ml plastic spoonful.

Children who find cod-liver oil unpalatable can be given halibut-liver oil in a very small dose since its concentration of vitamins A and D is approximately 20 to 40 times that of cod-liver oil. Each B.P. capsule of halibut-liver oil contains 11 μg of vitamin D and over 1,200 μg of vitamin A.

For severe cases needing 125 μg or more daily, synthetic calciferol is useful because the volume of cod-liver oil required to provide this dose may be excessive. For such patients the B.P. calciferol solution is satisfactory. It contains 75 μg of vitamin D per ml. In times of social upheaval, such as may be occasioned by war, floods or pestilence, when a young child may be seen once by an emergency medical service and perhaps not again for months, a single massive dose of vitamin D, e.g. 3·75 mg, can be given by mouth with reasonable safety and curative effects. For this purpose three B.P. strong calciferol tablets each containing 1·25 mg are suitable. A single dose of 3·75 mg can be given by intramuscular injection (0·5 ml of calciferol injection, B.P.C.) but this has no proved advantage over the oral route. The daily administration of small doses is the method recommended for normal practice, because of the danger of overdosage (p. 141).

CALCIUM PREPARATIONS. In addition to vitamin D, rachitic infants and children require an ample supply of calcium, the best source of which is milk. At least half a litre (about 1 pint) should be taken daily by a young child with rickets. For a severe case a supplement of calcium should also be given such as calcium gluconate, one to two tablets three times a day well chewed before swallowing. Each B.P.C. tablet contains 600 mg of calcium gluconate (53·5 mg of calcium). Alternatively, and preferably, one to two tablets of calcium gluconate effervescent (B.P.C.) can be dissolved in a glass of water three times a day. Each tablet contains 1 g calcium gluconate. When much larger amounts of calcium are required as may be the case in resistant rickets (see below), the malabsorption syndrome or osteoporosis, the Sandoz preparation of calcium gluconate effervescent tablets (Sandocal) can be given dissolved in a glass of water. The dose is one tablet three times a day. Each tablet contains 4·5 g of calcium gluconate (400 mg of calcium).

For emergency treatment of tetany (p. 653), calcium gluconate injection (B.P.) in 5-ml and 10-ml ampoules can be given by slow intravenous injection or intramuscularly in a dose of 10-20 ml. This supersaturated B.P. solution contains 1 g of calcium gluconate in 10 ml of water. For infants and young children the dose should be reduced to 300-600 mg of calcium gluconate.

GENERAL MEASURES. Vitamin D and diet are not the whole solution to the treatment of rickets. An attempt must be made to improve the hygienic environment of the child. This often requires the tactful education of the mother in better feeding practices and general care. Unnecessary clothing should be removed and if the child was previously confined indoors he should be allowed out as much as possible to enjoy the sunshine. This is particularly important in countries where supplements of vitamin D are not provided.

PROGRESS. The earliest evidence of healing in rickets is provided by radiological examination of the growing ends of the bones. The levels of calcium and phosphorus in the serum provide an inconstant and unreliable guide. A more constant change is a decrease in the raised serum alkaline phosphatase level but this does not usually occur for several weeks after treatment is initiated: the therapeutic dose of vitamin D should be continued so long as the phosphatase level remains elevated; thereafter it may gradually be reduced to the prophylactic dose of 10 micrograms daily.

Vitamin D Resistant Rickets. Occasionally cases of rickets are encountered which are resistant to ordinary therapeutic doses of vitamin D. The disease persists into late childhood ('late rickets') or even adult life, producing the clinical appearance of osteomalacia, unless adequately treated. One cause of this syndrome is a group of uncommon congenital disorders of the renal tubules in which phosphate reabsorption is defective, e.g. Fanconi syndrome (p. 582) and renal tubular acidosis. A similar state may sometimes arise as a conditioned deficiency resulting from malabsorption of vitamin D or from chronic renal failure in which renal formation of the active metabolite from cholecalciferol is impaired. Whatever the cause, treatment consists in giving large doses of vitamin D by mouth in the form of strong calciferol tablets (B.P.), together with calcium salts, e.g. one effervescent Sandocal tablet (B.P.C.) dissolved in a glass of water three times a day. The initial dose of calciferol may be 1·25-3·75 mg daily (1-3 B.P. strong calciferol tablets) but it should be reduced at the first suspicion of toxic symptoms.

Hypervitaminosis D. In the case of vitamin D it is possible to have too much of a good thing. Large doses are toxic and cause hypercalcaemia. The symptoms include nausea, vomiting, diarrhoea, drowsiness and signs of renal failure; metastatic calcification in the arteries, kidneys and other tissues may occur. Since renal damage may develop before clinical signs of toxicity appear, it is recommended that all patients on large doses of vitamin D should have their serum calcium level checked regularly at three-monthly intervals and if this is found to be above 5·5 mEq/*l* (11 mg/100 ml) it is an early indication of overdosage.

Prognosis. Rickets is not a fatal disease *per se*, but the untreated rachitic child is always a weakling owing to the risk of infections, notably bronchopneumonia. For some unknown reason the skeletal changes, if mild in degree, usually tend to heal spontaneously as the child gets older, but in severe cases pigeon chest, spinal curvature, knock knees, bow legs or pelvic deformities may persist. With early and sufficient treatment these changes are entirely avoided.

Prophylaxis. The provision of adequate milk for children, the clearing of slums, the building of new housing estates and smoke abatement schemes are basic prophylactic measures which must be continued. In addition mothers must be educated in the need to keep their infants and children in the sunshine as much as possible. Nevertheless, for reasons already stated and particularly in northern countries, the supply of the vitamin from this source is uncertain and attention must be paid to the dietary supply. It must be remembered that none of the common foods in a child's diet is a good source of vitamin D. Practical experience shows that the majority of children benefit by receiving a daily supplement of about 10 μg, preferably in the form of some natural source such as cod-liver oil, which also provides useful amounts of vitamin A. This is also advisable in sunny tropical countries if the mothers insist on keeping their infants wrapped in clothes during the first year of life. It seems reasonable that the supplement should be started within four weeks of birth because human and animal milk has a negligible content of vitamin D.

Before deciding on the prophylactic dose of cod-liver oil or other fish oil, it is necessary to consider how much vitamin D the infant is getting from other sources. Thus, if he is being brought up on a preparation of dried milk 'fortified' with vitamin D (e.g. British National Dried Milk which contains 2·5 μg per oz. of powder) the supplement of cod-liver oil should be small. Furthermore, it should be remembered that some proprietary cereal foods for infants are 'fortified' with vitamin D by the manufacturers as is British margarine.

Not only is there no advantage in giving infants and young children more than 10 μg of vitamin D daily *from all sources* for prophylactic purposes, but there is a distinct possibility that higher doses given over a long period may have harmful effects. The potential dangers of overdosage with vitamin D have been emphasised by the discovery that infantile hypercalcaemia is not such a rare condition as was formerly believed.

It should be noted, however, that the prophylactic dose of vitamin D for premature infants should be twice that for full-term infants and the supplement should be started within two weeks of birth. There has been divergence of view among paediatricians in the past about the length of time that the prophylactic administration of vitamin D should be continued. Obviously such features as the social and economic status of the parents and the climate in which the family lives are matters of importance. It seems reasonable to suggest that in temperate climates at least, a daily intake of about 10 μg should be continued summer and winter for the first five years of life.

Osteomalacia and Osteoporosis

These are two chronic disorders of the skeleton. Although they have a similar effect on the mechanical function of bone because they weaken the parts affected, their pathology, chemistry and treatment are different. For reasons given below it is possible that the distinction may not be so sharp, since calcium deficiency may be of aetiological importance in both diseases.

Osteomalacia, which means softening of bone, is primarily due to a deficiency of vitamin D, and to a lesser extent of calcium, or both. This results in a failure to lay down calcium and phosphorus in the organic matrix of bone. Hence the ratio of calcium phosphate to matrix is reduced.

Osteoporosis, which is an atrophy of bone, is believed to be due to defective formation of bone matrix which leads to a reduction in the total mass of bone. In other words osteoporosis may be defined as a disorder of too little bone of normal composition. In contrast to osteomalacia the ratio of calcium phosphate to matrix is normal.

New bone has to be formed in adults because, like other tissues, bone is continually and slowly turning over by resorption and replacement. Both osteoporosis and osteomalacia occur in old people in all countries.

Osteomalacia

Aetiology and Geographic Distribution. Osteomalacia is the adult counterpart of rickets. In its fully developed form as it occurs in women in purdah in oriental countries, it causes great deformity and suffering. Such women are of the child-bearing age who live on poor cereal diets devoid of milk, who are kept indoors and seldom see the sun, and who become depleted of calcium by repeated pregnancies. In oriental countries the onset often coincides with the first pregnancy, a remission occurring after delivery, but symptoms return with each succeeding pregnancy. It has been shown in Scotland and in other countries that osteomalacia is a relatively common disease in old people, especially women, and that it occurs more frequently than scurvy or rickets. The disease may be due to malabsorption from any cause, including previous operations on the gastrointestinal tract especially partial gastrectomy, or to direct dietary deficiency of vitamin D. Chronic renal disorders are a less important cause of the disease.

Epileptics who have to take anticonvulsants for years are likely to develop osteomalacia (or rickets in children). These drugs probably increase the catabolism of cholecalciferol by liver microsomes.

Pathology. The biochemical changes in the blood are essentially the same as those in rickets. The progressive decalcification of the bones leads to the replacement of bony substance with soft osteoid tissue. This process goes on all over the skeleton, but the effects are greatest in the spine, ribs, shoulder girdle, pelvis and lower limbs. A combination of osteomalacia and osteoporosis is not uncommon.

Clinical Features. Skeletal pain is usually present and persistent and ranges from a dull ache to severe pain. Sites frequently affected are the ribs, sacrum, lower lumbar vertebrae, pelvis and legs. Bone tenderness on pressure is common. Muscular weakness is often present and the patient may find difficulty in climbing stairs or getting out of a chair. A waddling gait is not unusual. Tetany may be manifested by carpopedal spasm and facial twitching. Spontaneous fractures may occur, independent of the pseudo-fractures described below. The therapeutic response to vitamin D is usually dramatic.

Diagnosis. The early symptoms may be mistaken for those present in osteoporosis or rheumatic disorders. The clinical examination must be supplemented by a careful enquiry into adverse social, economic and dietary factors which may be present. A search should be made for evidence of malabsorption or of renal disease. In addition biochemical tests, including serum calcium, phosphorus and alkaline phosphatase determinations and radiological examination of the skeleton should be undertaken. Histological examination of stained undecalcified sections of bone obtained by biopsy may be required as this shows unequivocally the presence of excess osteoid tissue.

Radiological examination shows rarefaction of bone and commonly translucent bands (pseudo-fractures, Looser's zones), often symmetrical, at points submitted to compression stress. Common sites are the ribs, the axillary borders of the scapula, the pubic rami and the medial cortex of the upper femur. Looser's zones are diagnostic of osteomalacia.

Treatment. This is essentially the same as for rickets when osteomalacia is primarily due to defective intake, namely 25 to 125 μg vitamin D daily. If there is evidence of malabsorption the dose should be 1·25 mg daily and it may have to be given intramuscularly at weekly intervals. If the disease is secondary to renal disorders double or treble this dose may be required. Maintenance treatment with vitamin D will be required for all cases of osteomalacia in which the cause cannot be removed. In addition a good diet should be given which includes milk, eggs, butter or margarine. This may be difficult or impossible under the conditions in which the disease arises in the East. In all cases of osteomalacia and especially when both osteoporosis and osteomalacia are present a supplement of calcium should be given orally, namely one to two tablets of calcium gluconate (B.P.) thrice daily or preferably one Sandocal tablet (p. 140) three times a day in a glass of water. Within four to eight weeks of starting treatment the pain and weakness has usually disappeared. The decision to reduce or discontinue the dose of vitamin D and calcium is based on the improvement in the clinical features and the disappearance of biochemical and radiological abnormalities. The dangers of vitamin D intoxication should be kept in mind (p. 141).

Prevention. Once major deformities are established they cannot be corrected by diet or drugs but only by an orthopaedic surgeon. Hence the great importance of prevention and of early and correct diagnosis and proper treatment. Free access to sunshine and an adequate intake of dairy produce, supplemented when necessary with fish-liver oil, will prevent nutritional osteomalacia. Particular attention to these prophylactic measures should be given to elderly inmates of geriatric and mental hospitals and to old people living alone and whose exposure to sunshine is limited and also to those who have had gastric surgery. It is worth noting that margarines are fortified with vitamin D in Britain: one ounce (28 mg) contains nearly 2·5 μg, the adult daily requirement. This is the most reliable food source of the vitamin for adults in Britain. With improved education and better standards of living the disease is now much rarer in many Asian towns where previously it was common.

Epileptic patients on long-term anticonvulsant therapy should be given prophylactic doses of vitamin D and watched for early signs of osteomalacia.

Osteoporosis

Osteoporosis is the disease of bone most frequently encountered in clinical practice. It may be a localised or generalised disease. The most common cause of the former is immobilisation but it may also arise as a result of inflammation or neoplasm of bone. Disuse removes the stresses and strains which stimulate the osteoblasts to lay down new bone, whilst the osteoclasts continue to remove calcium salts. This happens when movement is restricted by splinting, inflammation or pain, or when a patient is confined to bed. Extra provision of nutrients in the diet cannot prevent this process.

Generalised osteoporosis represents a non-specific reaction of the skeleton to a wide variety of stimuli. It is, however, a clinico-pathological entity since it can be differentiated from other generalised diseases of bone such as osteomalacia and osteitis fibrosa (hyperparathyroidism) by its characteristic clinical, radiological and pathological features.

Aetiology. The incidence of generalised osteoporosis rises in both sexes with advancing age. The density of the bones has been shown to decline in all people from the age of 40 to 50 onwards; the process is more marked in women. This physiological atrophy of bone makes it difficult to decide on the value of any form of treatment and the validity of the terms used to describe the various types of osteoporosis, e.g. idiopathic, secondary, post-menopausal, senile, etc. However it seems probable that those patients who develop the clinical features of osteoporosis before the age of 50 to 60 have had the physiological ageing process *accelerated* by factors known or unknown and in particular by hormonal deficiency and calcium deficiency. Physical inactivity is also a contributing factor.

HORMONAL DEFICIENCY. The frequency with which generalised osteoporosis develops in women after the menopause and the fact that it is much more common in women than in men has led to the belief that a failure of sex hormone secretion may be one of the factors concerned with the production of this type of osteoporosis. The similar condition in men often described as senile osteoporosis, is thought to be related to diminished androgen formation.

CALCIUM DEFICIENCY. A high faecal calcium and low calcium absorption have been reported in osteoporosis by some workers. This suggests that a reduced calcium absorption or failure in the normal compensating ability of the kidneys to decrease urinary excretion of calcium may be of aetiological importance, especially if the intake of calcium in the diet has been low for many years. However, other authorities deny that there is a negative calcium balance in most cases. In addition they are doubtful if dietary deficiency of calcium plays any significant role in the causation of the human disease. Studies with the isotopes of calcium and strontium have failed to unravel the mystery of the aetiology of osteoporosis, nor have they helped in its diagnosis or treatment.

IMMOBILISATION AND INSUFFICIENT PHYSICAL ACTIVITY. Orthopaedic surgeons are well aware that immobilisation of a limb for any reason leads to rapid demineralisation of the bones. It is therefore probable that an important factor which accelerates the normal loss of bone with age and leads to generalised osteoporosis is insufficient physical activity from any cause including chronic disabling diseases such as rheumatoid arthritis.

Types of Osteoporosis

IDIOPATHIC OSTEOPOROSIS. Osteoporosis may occur rarely in juveniles and in adults between 20 and 40 years without any apparent cause. A period of increased osteoporotic activity develops and may last for many months with the production of features identical to those occurring in classical osteoporosis in old people. This activity usually remits eventually and clinical and radiological improvement occurs even without treatment.

The age-group of 60 years and over is the one in which most of the cases of osteoporosis are seen in practice. Such cases are usually the end-result of the physiological ageing process but in some of them self-limiting acute exacerbations of the disease occur with negative calcium balances for which no adequate explanation is available.

OSTEOPOROSIS DUE TO CAUSES KNOWN OR SUSPECTED. The most important of these causes are (1) hypogonadism in both males and females, (2) hyperadrenocorticism as occurs in Cushing's syndrome or after prolonged treatment with adrenal corticosteroids, (3) acromegaly, (4) prolonged calcium deficiency.

Other disorders which are less frequently associated with osteoporosis are scurvy, rheumatoid arthritis, protein malnutrition, hepatic disease of long standing, uncontrolled diabetes, thyrotoxicosis and chronic alcoholism.

Clinical Features. There may be no symptoms despite clear-cut radiological changes or there may be much disability. Episodes of severe bone pain are usually due to fractures of the brittle bones and may occur after minimal trauma. Two characteristic fractures are Colles fracture of the lower end of the radius, common in women aged 60 to 70 years, and fracture of the neck of the femur, which usually occurs in either sex over the age of 70 years. Healing of fractures is not impaired in osteoporosis and pain usually subsides after immobilization as healing takes place.

Pain due to fractures of the vertebrae may radiate round the trunk, to the buttocks or down the legs. More persistent backache, often described as lumbago, is a secondary and frequently late feature of osteoporosis and is due in part to progressive vertebral collapse and in part to osteoarthrosis. Pain occurs much more rarely in the sternum, pelvis, ribs and long bones; *persistent* pain elsewhere in the skeleton is not a feature of osteoporosis, but is more characteristic of osteomalacia, Paget's disease or skeletal metastases. The persistent nagging continuous pain in osteomalacia which is due to strain on tender soft bone, contrasts with the intermittent severe attacks of pain followed by periods of improvement which are so characteristic of osteoporosis.

Patients with osteoporosis are usually surprisingly well and lack the features of a serious systemic disease. Loss of stature due to shortening of the trunk is seen when there is compression or collapse of several vertebrae. Later a deformed shrunken thoracic cage may result.

Biochemistry and Histology. Calcium, phosphorus and alkaline phosphatase levels in the blood are normal, in contrast to other generalised disorders of bone.

The histological appearance of osteoporotic bone is qualitatively normal in contrast to osteomalacia where there is a failure of mineralisation of bone matrix and evidence of abnormally large amounts of osteoid tissue.

Radiological Appearances. These play an important part in diagnosis. The principal radiological findings are (1) loss of bone density, (2) reduction in number and size of trabeculae, (3) thinning of the bone cortex, and (4) the vertebral bodies first become biconcave at the upper and lower surfaces. Later collapse of whole vertebrae produces a wedge-shaped appearance. In contrast, all the vertebrae in osteomalacia, being softer than normal, tend to be uniformly involved, while wedging of vertebrae is uncommon. Radiological evidence of osteoporosis may be found in other bones as well as the spine; thinning of the cortex is the most important sign.

Differential Diagnosis. The differential diagnosis from osteomalacia is discussed on page 143.

Treatment. Treatment remains unsatisfactory, especially in those cases in which the cause is uncertain or unknown. All that can be expected is an arrest of the progress of the disease. The most favoured method of treatment at the present time is either the prescription of sex hormones or the administration of a high intake of calcium. The value of treatment with fluoride is being investigated. The natural history of the disease makes it difficult to evaluate any method of treatment because the patient often seeks medical advice on account of pain resulting from a fracture and this spontaneously remits following rest. Any drug prescribed at that time is likely to be given the credit for achieving this result.

If treatment with sex hormones is advised for post-menopausal women because of pain and frequency of fractures, stilboestrol is recommended in a dose of 1 mg a day. A reasonable alternative to this would be ethinyl oestradiol 0·05 mg once daily. It should be pointed out to patients that this is physiological substitution for ovarian failure, and the drugs should be given in courses lasting for three weeks at a time and should then be withdrawn for one week before resuming treatment. The patient should be warned that she should not be surprised if menstrual bleeding occurs on withdrawal. The need for continuing treatment on these lines should be reviewed after an interval of 12 months in view of the misgivings which gynaecologists have about the relationship between administered oestrogens and uterine carcinoma. For senile osteoporosis in males methyltestosterone may be given continuously in a dose of 25-50 mg a day sublingually. Although treatment with sex hormones is often followed by relief of pain whether they have any effect on the mineralisation of bone is uncertain.

The value of anabolic agents such as norethandrolone (Nilevar) or nandrolone phenylpropionate (Durabolin) is doubtful.

Whatever else is prescribed, all patients with osteoporosis should receive at least the recommended intake of dietary calcium, daily, preferably as milk and/or cheese. Half a litre of milk provides about 20 g of protein and 600 mg of calcium. Physiological doses of vitamin D (p. 139) are needed to ensure its absorption. For those in whom it is believed that an improvement in the calcium balance can be obtained by a high calcium intake, treatment with calcium tablets to give 1 to 2 grams *as calcium* per day is given as described on page 140.

It is essential to get the patient up and about as much as possible. Fortunately the majority of osteoporotic fractures do not require to be treated by prolonged bed rest or immobilisation which would aggravate the bone atrophy. Analgesics will be required for the treatment of severe attacks of pain and antibiotics for pulmonary infections which are liable to occur. Obesity must be prevented at all costs. If there is much backache a light spinal brace may help.

Prognosis. Despite the disappointing effects of all forms of treatment, the prognosis for length of life is good and few persons die of the disease. Most patients keep well despite intermittent attacks of severe pain due to fractures. Some patients, particularly in the younger age-groups, pass through a phase lasting several years in which several fractures may occur, but subsequently stabilise and have little further trouble.

Prevention. Since the cause of osteoporosis is uncertain and since demineralisation of the skeleton is known to begin at the age of 40 to 50 although symptoms may not appear for many years, its prevention is obviously a formidable task. An active life and a well-balanced diet containing 0·5 *l* of milk daily to ensure an adequate intake of protein and calcium, are certainly worthwhile preventive measures. It is most important that middle-aged and elderly persons with chronic diseases do not allow their ill-health to immobilise them. All such patients must be encouraged to take exercise as much as their disability permits.

VITAMIN K

Vitamin K is required for the formation in the liver of prothrombin, which is necessary for the normal clotting of blood (p. 756). It exists in nature in two forms, vitamin K_1 and vitamin K_2. Since the latter is not important in medical practice it need not be discussed further. Natural vitamin K_1 (phytomenadione) is soluble in fat solvents but only slightly in water.

Dietary Sources. Vitamin K is present in fresh dark-green vegetables, such as cauliflower, spinach and lucerne. All foods of animal origin, including fish-liver oils, are poor sources unless they have undergone extensive bacterial putrefaction. Adequate amounts are normally supplied in the average diet and by bacterial synthesis within the intestine.

Therapeutic Uses. Vitamin K_1, by mouth or injection, is indicated in the following conditions: (1) haemorrhagic disease of the newborn (p. 764): (2) obstructive jaundice (p. 541); (3) malabsorption (p. 492): and (4) overdosage with anticoagulants, warfarin or phenindione (p. 765).

VITAMIN C—ASCORBIC ACID

Chemistry and Physiological Action. Ascorbic acid is a simple sugar. It is the most active reducing agent found in living tissues and is easily and reversibly oxidised to dehydro-ascorbic acid. Its highest concentration in the body is in the adrenal cortex. Burns and severe injuries lead to a loss of ascorbic acid from the cortex, as does the injection of corticotrophin. The presumption, therefore, is that ascorbic acid is intimately concerned in bodily reactions to stress, though in a manner as yet obscure. Man is one of the few animals that cannot synthesise his own ascorbic acid from glucose.

Ascorbic acid is very easily destroyed by heat, alkalis such as sodium bicarbonate, traces of copper or by an oxidase liberated by damage to plant tissues. Ascorbic acid is very soluble in water. For these reasons many traditional methods of cooking reduce or eliminate it from the diet. A satisfactory daily allowance is 30 mg.

Dietary Sources. Citrus fruits, blackcurrants, berries and green vegetables are the richest sources. The importance of a particular food as a source of a vitamin depends on the amount eaten. Thus, in Britain, potatoes are more important than watercress even though they have a much lower content of vitamin C. Dried cereals and pulses contain no ascorbic acid. Foods of animal origin contain very little except for liver and glandular tissue.

Pathology of Ascorbic Acid Deficiency. Ascorbic acid deficiency results in defective formation of collagen in connective tissue, defective intercellular cement, defective dentine in teeth, defective osteoid tissue in bone and subnormal platelet stickiness. Capillary haemorrhages, delayed healing of wounds and (during growth) defective formation of teeth and bones result. In adults the teeth may become loose.

Scurvy

Aetiology. In 1497 Vasco da Gama sailed round the Cape of Good Hope and established a trading centre on the Malabar coast. Scurvy occurred among his crew on the voyage and 100 out of his 160 men died. For the next 300 years scurvy was a major factor determining the success or failure of all sea ventures until it was recognised that scurvy results from the prolonged consumption of a diet devoid of fresh fruit and vegetables. The principal deficiency in such a diet is the lack of ascorbic acid which is responsible for the characteristic features of the disease. Nevertheless such diets are likely to be deficient also in other nutrients such as iron, vitamin A and folic acid and sometimes protein. Thus, although ascorbic acid will relieve the predominant signs of the disease, it does not always cure the patient. Sporadic cases of scurvy continue to arise in Britain in infants as a result of ignorance, poverty and maternal neglect and also amongst old people, especially males living alone with neither the opportunity nor the aptitude to feed themselves properly.

Scurvy appears to be a rare disease in infants and children in most sub-tropical countries but it may be seen in infants who are weaned prematurely. It is more likely to occur in arid regions of the world in times of drought, as in Arabia and parts of India after a failure of the monsoon rains.

Clinical Features. ADULT SCURVY. The pathognomic sign is the appearance of the gums which are swollen and spongy particularly in the region of the papillae between the teeth, sometimes producing the appearance of 'scurvy buds'. These may be so extensive that they project beyond the biting surface of the teeth and almost completely conceal them. The swollen gums are livid in colour and bleed on the slightest touch. There is always some infection; indeed this seems necessary for the production of the scorbutic gingival appearances since human volunteers suffering from ascorbic acid deficiency did not develop it if their gums were previously healthy. Associated with the infection there is an offensive foetor. In patients without teeth the gums appear normal.

The first sign of cutaneous bleeding is often to be found on the lower thighs, just above the knees. These haemorrhages are perifollicular—tiny points of bleeding around the orifice of a hair follicle. For some time beforehand the follicle can be seen to be raised above the general surface of the skin, giving the appearance of folliculosis, which is non-specific. The condition in scurvy can be distinguished by its appearance from the follicular keratosis sometimes associated with vitamin A deficiency. In the latter condition there is usually a horny plug of keratin projecting from the orifice of the hair follicle. In scurvy there is a heaping-up of keratin-like material on the surface around the mouth of the follicle, through which a deformed 'corkscrew' hair characteristically projects. Perifollicular haemorrhages may subsequently appear on the buttocks, abdomen, legs and arms; they are often followed by petechial haemorrhages, developing independently of the hair follicles, due to rupture of capillary vessels. Such purpuric spots are usually first seen on the feet and ankles. Thereafter large spontaneous bruises (ecchymoses) may arise almost anywhere in the body, but usually first in the lower extremities, producing the characteristic 'woody leg'. Haemorrhage may occur into joints, into a nerve sheath, under the nails or conjunctiva, into the gastrointestinal tract or there may be epistaxis. Scurvy can present with any of these features. By the time the disease is fully developed the patient is usually anaemic (p. 733).

Another characteristic of scurvy is that fresh wounds fail to heal—a feature that the surgeon has to bear in mind. Osteoporosis of the spine has been reported in prolonged cases in adults.

Before the changes in the gums and skin appear, the patient has usually felt feeble and listless for some weeks or months. If hard work is expected of him, he may have been suspected of malingering, through absence of clinical signs suggesting disease and hence the gravity of his condition may not have been appreciated. Yet he may die suddenly and without warning apparently from cardiac failure.

INFANTILE SCURVY. The main clinical features are lassitude, anaemia, painful limbs and enlargement of the costochondral junctions. Until the teeth have erupted, scorbutic infants do not develop gingivitis. When this occurs the gums have the classical appearance of 'scurvy buds'. The first sign of bleeding is usually a large subperiosteal haemorrhage immediately overlying one of the long bones—frequently the femur—producing the characteristic 'frog-legs' position. This gives rise to intense pain, especially on movement. The infant may cry continuously and agonisingly, and scream even louder when lifted.

Diagnosis. The distinctive appearance of the gums must be distinguished from other causes of gingivitis. ① In non-specific gingivitis (p. 444) there are usually accumulations of tartar on the teeth, with retraction of the gum margin. The inflamed rim of the gums is bright red in colour, in contrast to the cyanotic appearance in scurvy, and there is usually much less swelling. In ② Vincent's stomatitis (p. 444) the gums are acutely inflamed, ulcerated and painful: here again the bright red appearance of the lesions is distinctive. ③ Poisoning with lead produces a gingivitis in which the gum margin is stained blue but there is usually little swelling. 4 Hydantoin derivatives used in the treatment of epilepsy may cause marked hypertrophy of the gums, but they preserve their normal colour and do not bleed. The diagnosis of scurvy is most difficult in people who are edentulous, for then the clinician does not have the changes in the gums to guide him.

The perifollicular haemorrhages of scurvy are distinctive in appearance but if only petechiae are visible, other causes of purpura must be excluded (p. 759).

The dietary and social history is invaluable in establishing the diagnosis in doubtful cases. Old solitary people may insist that they fend very well for themselves, but careful questioning, or an inspection of the larder, will reveal that they do not bother to purchase fresh fruit or vegetables. In other instances the proper foods may be purchased but they are so badly cooked that in fact the diet is made scorbutic.

Scurvy in infants and children may sometimes be mistaken for rheumatic fever or osteomyelitis, because of the pain caused by a subperiosteal haemorrhage in immediate relation to one of the long bones. The refusal of the child to use one leg may cause the disease to be mistaken for poliomyelitis.

Special Investigations. Ascorbic acid can be estimated with relative ease in blood plasma. This is useful only in excluding the diagnosis since the blood level of the vitamin falls to very low levels long before the disease develops. A better index of the tissue reserves of the vitamin is its concentration in the white blood cells or the platelets. If this is very low, the diagnosis of scurvy is practically certain.

Treatment. Because of the danger of sudden death, synthetic ascorbic acid should be given at once in adequate amounts. Parenteral treatment has no advantage over oral administration. The aim should be to saturate the body with ascorbic acid with as little delay as possible. The normal body contains about 1·5 g of the vitamin, so that a dose of 250 mg by mouth four times daily should achieve this within a few days, despite a considerable loss in the urine which quickly follows each dose.

Scurvy sometimes occurs among people far removed from supplies of synthetic ascorbic acid (e.g. among prisoners of war); in such situations valuable therapeutic effects are obtained by the use of natural sources of the vitamin such as fresh fruit and vegetables, sprouting peas or extract of pine needles (see below).

Once the danger of sudden death is averted, attention should be paid to correcting the general deficiencies of the patient's former diet. A liberal diet, including fresh fruit and as much properly cooked vegetables as are available and the patient will accept, should be given. If the patient is anaemic iron and sometimes folic acid are indicated.

Prognosis. With adequate treatment no patient dies of scurvy and recovery is usually rapid and complete.

Prevention. In Britain the prevention of scurvy in infants has been accomplished by the better education of mothers and helped by the distribution of cheap, concentrated orange juice of standard ascorbic acid content. Fruit juice should be given, especially to bottle-fed infants, for the first two years of life.

No simple administrative means has so far been found of preventing scurvy among the old and solitary, who are largely unresponsive to education. Should the physician be unsuccessful in achieving the dietetic aims discussed above, he should at least insist on the patient taking one 25-mg tablet of synthetic ascorbic acid daily. Alternatively a massive dose can be given at longer intervals —say 500 mg on the first day of every month. This method is justified because patients who are careless about diet are nearly always defaulters when daily medication is prescribed.

Special provision against scurvy is desirable for any group of people living on packed, preserved rations for any length of time such as explorers or armed forces operating in a barren territory. Synthetic ascorbic acid tablets are invaluable under such conditions. In default of such supplies antiscorbutic remedies can often be prepared from green herbs on the spot. Scurvy grass (*Cochlearia officinalis*), which grows on seashores, and infusions of pine needles are traditional remedies. In times of drought when fresh vegetables are not available many lives have been saved, particularly in India, by the organised distribution of sprouting peas and beans. The germination is produced by spreading the dried pulses under wet cloths.

ASCORBIC ACID AND THE COMMON COLD. It has been claimed that ascorbic acid in doses of 1-2 g daily will prevent the common cold. If it does, this is a pharmacological and not a vitamin effect as coryza is not a manifestation of scurvy. It is inadvisable for people to dose themselves with large quantities of ascorbic acid as this favours the formation of oxalate stones in the urinary tract and could have other adverse effects.

THE VITAMIN B COMPLEX

This group of water-soluble vitamins includes thiamin, niacin, riboflavin, pyridoxine, vitamin B_{12} and folate. Deficiencies occur in areas where undernutrition is prevalent and are often multiple.

The vitamins of the B complex are grouped together (although unrelated chemically) because they occur together in foods that are rich in cellular material with an active metabolism (e.g. yeast, liver). The vitamins of the B complex are essential parts of specific enzyme systems on which cellular metabolism depends. Thus thiamin pyrophosphate is cocarboxylase, which is concerned with the removal of pyruvic acid in the catabolism of carbohydrate. Riboflavin is an important component of the flavoproteins which play an essential role in tissue oxidation. Niacin is part of NAD and NADP, which are also concerned in tissue oxidation.

Other components of the vitamin B complex needed by certain animals (e.g. pantothenic acid, biotin) also have enzymic properties and certainly take part in the metabolism of human tissues, but there is no satisfactory evidence that any clinical disorder results from their deficiency except when highly artificial diets have been given.

THIAMIN

(VITAMIN B_1)

Chemistry and Physiological Action. Thiamin salts are readily soluble in water but not in fat. Thiamin pyrophosphate (TPP) is an essential coenzyme for the decarboxylation of pyruvate to acetyl coenzyme A. This is the bridge between anaerobic glycolysis and the tricarboxylic acid (Krebs) cycle. TPP is also the coenzyme for transketolase in the hexose monophosphate shunt pathway and for decarboxylation of α-ketoglutarate to succinate in the Krebs cycle. Consequently when thiamine is deficient (*a*) the cells cannot utilise glucose aerobically; this is likely to affect the nervous system first, since it depends entirely on glucose for its energy requirements; (*b*) there is accumulation of pyruvic acid and of lactic acid derived from it, which produce vasodilatation and increase cardiac output. High carbohydrate diets predispose to and aggravate thiamin deficiency.

In man thiamin deficiency can produce cardiomyopathy and/or peripheral neuropathy and/or encephalopathy. These occur in various combinations and clinical settings in the following diseases:

1. Wet beriberi (beriberi heart disease) and thiamin-responsive alcoholic cardiomyopathy.
2. Dry beriberi and alcoholic peripheral neuropathy.
3. Infantile beriberi.
4. Wernicke's encephalopathy (cerebral beriberi) and Korsakoff's psychosis.

Dietary Sources. Pulses, pork, liver, nuts, the germ of cereals and yeast, are the only rich sources. Dried brewer's yeast, yeast extract (Marmite) and the bran of rice and wheat have all been used in the treatment of beriberi. Green vegetables, roots, fruits, flesh foods and dairy produce (except butter) contain small amounts of the vitamin. It is not found in butter or in vegetable or animal oils. In the refining of sugar and many cereal products (wheat, rice) nearly all the naturally occurring vitamin may be removed; there is also none in spirits.

As thiamin is readily soluble in water, considerable amounts may be lost when vegetables are cooked in an excess of water which is afterwards discarded. It is relatively stable below 100° C. provided that the medium is slightly acid, as in baking with yeast. But if baking powder is used, or if soda is added in the cooking of vegetables, almost all the vitamin may be destroyed. The loss of thiamin in the cooking of an ordinary mixed diet is usually around 25 per cent. Modern processes for freezing, canning and dehydrating food result in only small losses. Unlike vitamin A, thiamin is not stored in the body to any appreciable extent; hence symptoms due to deficiency may develop within a few weeks.

Therapeutic Uses. Thiamin is life-saving in the treatment of cardiovascular and infantile beriberi and Wernicke's encephalopathy as discussed below. It may be given, though without expectation of dramatic results, in cases of nutritional neuropathy. The value of synthetic thiamin, either alone or in combination with other vitamins, as a general tonic or appetiser, is supported by no good scientific evidence.

Beriberi

Beriberi is a nutritional disorder formerly widespread in South and East Asia. The word comes from the Singhalese language and means 'I cannot', signifying that the patient is too ill to do anything. It has almost disappeared from prosperous Asian countries such as Japan, Taiwan and Malaysia and from big cities such as Hong Kong, Manila and Singapore. The frequency with which absence of knee jerks and the presence of tenderness of the calf muscles has been noted in nutritional surveys undertaken in remote country regions where the disease is endemic, suggests that a mild to moderate deficiency of thiamin is not uncommon. Oriental beriberi is usually caused by eating diets in which most of the calories are derived from polished, i.e. highly milled rice. The disorder is often precipitated by infections, hard physical labour or pregnancy and lactation. The clinical picture usually suggests the presence of a multiple nutritional disorder, although lack of thiamin produces the predominant clinical changes.

Today in Britain and North America occasional cases of beriberi heart disease are seen, usually in alcoholics who have been consuming little but alcohol for some weeks.

Chemical Pathology. Owing to a lack of thiamin, carbohydrates are incompletely metabolised and there is an accumulation of lactic and pyruvic acids in the tissues and body fluids. The local accumulation of these metabolites causes dilatation of peripheral blood vessels, as in normal subjects. In beriberi this vasodilatation may be extreme, so that fluid leaks out through the capillaries, producing oedema. At the same time the blood flows rapidly through the dilated peripheral circulation. The heart, which is already embarrassed through lack of thiamin needed for the normal metabolism of carbohydrate in the heart muscle, dilates and 'high output' heart failure further accentuates the oedema. Sudden death may result from acute myocardial exhaustion.

In dry beriberi the level of blood pyruvate is usually within normal limits.

Morbid Anatomy. In wet beriberi the heart at autopsy is greatly dilated, especially on the right side: there is general oedema of the tissues and serous effusions into the body cavities including the pericardium. Microscopic examination usually shows loss of striation of myocardial fibres, which are also finely vacuolated and often fragmented and separated by oedema.

In dry beriberi there is severe wasting of muscles. In long-standing cases there is degeneration and demyelination of both sensory and motor nerves. The vagus and other autonomic nerves may be affected. Degenerative changes both in the tracts and in grey matter of the cord are found, but these are usually not so marked as in the peripheral nerves.

Clinical Features. The *early* symptoms and signs are common to wet and dry beriberi. The onset is usually insidious, though sometimes precipitated by unwonted exertion or a minor febrile illness. At first there is anorexia and ill-defined malaise, associated with heaviness and weakness of the legs. This may cause some difficulty in walking. There may be a little oedema of the legs or face and the patient may complain of precordial pain and palpitations. The pulse is usually full and moderately increased in rate. There may be complaints of 'pins and needles' and numbness in the legs. The tendon jerks are usually sluggish, and the calf muscles may be slightly tender on pressure. Hypoaesthesia or anaesthesia of the skin, especially over the tibiae, is common. Such a condition may persist for months or even years with only minor alterations in the symptoms. In areas where beriberi is endemic it is often extremely common. The patients are only mildly incapacitated and many continue to earn their living even as manual labourers, but at a very low level of efficiency. At any time this chronic malady may develop into either of the severe forms.

WET BERIBERI. A diet relatively sufficient in calories and carbohydrate and lacking in thiamin is the essential cause of wet beriberi. The patient thus often appears well fed. Oedema is the most notable feature which may develop rapidly and involve not only the legs but also the face, trunk and serous cavities. Palpitations and breathlessness are marked. There may be pain in the legs after walking. This is probably due to the accumulation of lactic acid. It is similar to that which occurs physiologically in the muscles of a runner and pathologically as a result of an insufficient blood supply in intermittent claudication. The heart is enlarged. There is usually tachycardia and an increase in pulse pressure. While the circulation is well maintained, the skin is warm owing to the vasodilatation; as heart failure advances, the skin becomes cold and cyanotic. The mind is usually clear. Electrocardiograms often show no changes except sinus tachycardia but in some cases there are inverted T waves or evidence of disturbed conduction.

DRY BERIBERI. The essential feature is a polyneuropathy (p. 167). The early symptoms and signs are described on page 154. The muscles become progressively weak and wasted, and walking becomes increasingly difficult. The thin, even emaciated patient needs at first one stick, then two, and may finally become bedridden. The disease is essentially a chronic malady, which may be arrested at any stage by improving the diet. Bedridden patients and those with severe cachexia are very susceptible to infections. When bacillary dysentery or tuberculosis accompany dry beriberi, a fatal result may rapidly occur unless prompt and efficient treatment is given. Patients with dry beriberi are always liable to a sudden onset of oedema which may be due to a variety of dietary causes, e.g. lack of protein, calories or thiamin.

INFANTILE BERIBERI. This is seen in areas where adult beriberi is endemic. It occurs in breast-fed infants, usually between the second and fifth months. Although the mothers of such infants must have been eating a diet and secreting milk with a low thiamin content, classical signs of beriberi are stated to be absent in 50 per cent of them. The illness usually starts acutely and is rapidly fatal, from cardiac failure, if not promptly treated. The mother may have noticed that the infant is restless, often cries, is passing less urine than normal and shows signs of puffiness. The infant then may suddenly become cyanosed with dyspnoea and tachycardia and die within 24 to 48 hours. Other serious signs are convulsions and coma. One characteristic sign, usually encountered only in severe cases, is partial or complete aphonia usually preceded by the infant's cry becoming thin with a plaintive whine. In the chronic form a state of marasmus develops due to a general failure of nutrition often associated with anorexia, vomiting and diarrhoea, but there is little evidence of structural disease in the nervous system.

Infantile beriberi was formerly the chief cause of death in infants between 2 and 6 months of age in regions where the disease was endemic, and it may still be an important cause in certain isolated rural areas in South-East Asia.

WERNICKE'S ENCEPHALOPATHY. This syndrome, which is described on page 896, may be associated with other forms of beriberi but in Europe and the USA most commonly occurs in alcoholics.

Differential Diagnosis. In endemic areas the diagnosis of beriberi is usually not difficult. Outside these areas the diagnosis should be considered if there is a history of a poor diet associated with alcoholism or based on polished rice or other refined cereal.

In mild and chronic cases there may be few or no physical signs and the diagnosis may have to depend on the interpretation of symptoms and the dietary history, often inaccurately described. In prisons and labour forces, such patients may be accused of malingering. The symptoms also closely resemble those of anxiety states.

The oedema of wet beriberi must be distinguished from that associated with hepatic and renal disease, cardiac failure and PCM. The warm extremities in cardiac beriberi and the absence of protein in the urine are useful diagnostic points. Famine oedema should seldom be a diagnostic difficulty if a proper dietary history is taken. Wet beriberi and famine oedema seldom occur together in adults.

Cardiovascular beriberi must be distinguished from other causes of high output cardiac failure, notably hyperthyroidism and severe anaemia, both of which may produce many of the same clinical features. In severe beriberi heart disease there may be low output cardiac failure, which has to be differentiated from other causes of cardiomyopathy or myocarditis (p. 285). A history of alcoholism or a poor diet, often a surprisingly normal ECG and sometimes an associated peripheral neuropathy are valuable pointers to beriberi. If in doubt the patient should be given 50 to 100 mg of thiamin parenterally, preferably before other cardiac therapy has been started. Beriberi responds dramatically (p. 157).

The features of dry beriberi are sometimes indistinguishable on clinical examination from other forms of nutritional, infective and toxic polyneuropathy (p. 901). The differential diagnosis is accordingly based on the presence or absence of a history of nutritional deficiency and of such aetiological factors as alcoholism, the ingestion of toxic substances or an infective illness. The disease may be confused with neural leprosy in areas where this is endemic.

The diagnosis of infantile beriberi may be difficult. Neither oedema nor paralysis is an early sign and sudden death may occur before either is present. In cases of doubt the presence of minimal signs or symptoms of beriberi in the mother may decide the issue. A history of the sudden death of a previous child between the ages of 2 and 5 months is highly suggestive. In public health practice among a rice-eating community, a rise in death rate of infants should suggest the possibility that infantile beriberi has become endemic.

Laboratory Diagnosis. Pyruvic or lactic acids can be measured in the blood but they are not elevated in the more chronic forms of beriberi and if they are increased are not specific. The best laboratory test is measurement of transketolase activity in red cells with and without added thiamin pyrophosphate *in vitro*. The test requires fresh red cells and blood must be taken before thiamin treatment is started. A grossly abnormal result appears to be specific for beriberi or Wernicke's encephalopathy.

Treatment. WET BERIBERI. Treatment must be started as soon as the diagnosis is made, because fatal heart failure may occur suddenly. Complete rest is essential and thiamin should be given in amounts of 50 mg intramuscularly and continued for three days. Thereafter oral treatment in a dose of 10 mg three times a day should be continued until convalescence is established.

The prompt response of a patient with cardiovascular beriberi to thiamin is one of the most dramatic events of medicine. Within a few hours the breathing is easier, the pulse-rate slower, the extremities cooler and a rapid diuresis begins to dispose of the oedema. Within a few days the size of the heart is restored to normal. Muscular pain and tenderness are also dramatically improved. The ECG may show characteristic paradoxical changes while the patient improves. In a typical case the tracing is normal while heart failure is severe, then as recovery starts T wave inversions appear over the right ventricle for a few days.

DRY BERIBERI. The treatment is that of a nutritional polyneuropathy as described on page 167.

WERNICKE'S ENCEPHALOPATHY (p. 896). The ophthalmoplegia and nystagmus respond within hours to thiamin. The confusional state takes longer to clear, usually passing through the stage of Korsakoff's psychosis with confabulation for several days. Some impairment of memory may persist.

DIET AND OTHER MEASURES. Other deficiencies in the patient's diet may include protein, vitamin A, nicotinic acid and riboflavin. In the early stages the other B vitamins should be supplied, e.g. as tablets, and a good protein intake given. Thereafter a mixed diet with less emphasis on rice is needed. Pulses have a well-deserved reputation for curing and preventing beriberi. Any foods of animal origin that are available should be included. The diet can be supplemented usefully by natural sources of the entire vitamin B complex such as yeast or yeast extract, wheat germ or rice polishings.

In all forms of beriberi, preoccupation with dietary treatment should not divert attention from the necessity of good nursing, management of associated infections, physiotherapy and subsequent rehabilitation.

INFANTILE BERIBERI. The simplest way to treat infantile beriberi is via the mother's milk. The mother should receive 10 mg thiamin hydrochloride twice daily—in severe cases by injection. In addition the infant must be given thiamin. In cases of mild to moderate severity 10-20 mg of thiamin should be given intramuscularly once a day for three days, followed by oral treatment with 5-10 mg of thiamin twice a day for several weeks. With severe heart failure or convulsions and coma the initial dose of thiamin may be increased to 25 mg or even 50 mg given intravenously very slowly.

Prevention. In principle this is easy. All that is necessary in endemic areas is to prevent the production of over-milled rice or wheat. In practice, however, there are many difficulties in the control of milling processes and in persuading people to change their customary diet. Nevertheless improvement in milling practices has probably played an important part in reducing the incidence of beriberi.

Wherever possible, it is desirable to reduce the proportion of rice in the diet and encourage the growth of alternative crops and protective foods. Much can sometimes be done with small gardens properly cultivated. The substitution of parboiled rice for highly milled rice also greatly reduces the incidence of beriberi. Parboiling is the term used to indicate that unhusked rice has been steamed or boiled after preliminary soaking. If this is done before the rice is milled the greater portion of the vitamin B complex is conserved. Ignorance of the relative nutritional values of different foods is a contributory factor and can only be overcome by better education, improvement in social and economic conditions and establishing many more maternal and child health services.

NIACIN

Nicotinic Acid and Nicotinamide

Chemistry and Physiological Action. Nicotinamide is an essential part of the two important pyridine nucleotides, NAD and NADP which are hydrogen-accepting coenzymes for dehydrogenases at many steps in the pathways of glucose oxidation. NAD is also the coenzyme for alcohol dehydrogenase. Nicotinic acid (niacin) is readily converted in the body into the amide. For nutritional purposes the two have equal biological activity and are considered together in foods under the generic term 'niacin'. Both are water-soluble and resistant to heat.

Dietary Sources. Niacin is widely distributed in plant and animal foods, but only in relatively small amounts, except in meat (especially the organs), fish, wholemeal cereals and pulses. Removal of the bran in milling cereals reduces their niacin to low levels. Coffee is also a useful source. A cup of good coffee provides about 1 mg of niacin. In a normal Western European diet about half the nicotinic acid content is provided by meat and fish.

Cooking causes little destruction of niacin but considerable amounts may be lost in the cooking water and 'drippings' from cooked meat if these are discarded. In a mixed diet, from 15 to 25 per cent of the niacin of the cooked foodstuffs may be lost in this way. Commercial processing and storage of foodstuffs cause little loss.

A special feature of this vitamin is that it is normally synthesised in the body in limited amounts from the amino acid tryptophan. 60 mg of tryptophan yields 1 mg of nicotinamide. For this reason niacin equivalents in a diet are calculated by adding together the niacin plus $\frac{1}{60}$ of the tryptophan intake.

Pellagra

Pellagra is a nutritional disease endemic among poor peasants who subsist chiefly on maize (American corn). The greater part of the niacin in maize is in a bound form, niacytin, which is unavailable to the consumer. Moreover the principal protein of maize, zein, is deficient in the essential amino acid tryptophan.

History and Geographical Distribution. Pellagra is a relatively new disease, unknown to classical and mediaeval physicians. It has occurred all over the world, wherever maize is the staple cereal, e.g. the southern states of the USA, the Near East, Africa and South-East Europe and also in certain regions in India, Asia and Latin America. In recent years pellagra has disappeared from many countries where it was once endemic, and in areas where it remains the incidence is much less than formerly. An exception is southern Africa where big outbreaks occur in the spring and summer in certain Bantu areas. It accounts for a considerable proportion of patients admitted to the Bantu Mental Hospital in Pretoria.

Isolated cases of pellagra occur among people who are not dependent on maize. It is found as a complication of chronic alcoholism and has been reported in patients with renal failure on very low protein diets which had not been supplemented with B complex vitamins. Any chronic disease of the gastrointestinal tract, leading to malabsorption, may result in the development of pellagra. In the rare inborn error of metabolism, Hartnup disease, tryptophan absorption is impaired and there is a pellagrous dermatitis with neurological abnormalities which respond to nicotinamide.

Chemical Pathology. N-methylnicotinamide, a normal excretory product of nicotinamide appears in decreased amounts in the urine. Reduced plasma tryptophan has been reported in fasting blood. There may be anaemia and hypoalbuminaemia due to associated dietary deficiencies.

Morbid Anatomy. In addition to the dermatitis, the mucous membranes of the mouth, tongue, oesophagus, stomach, vagina and colon usually show abnormal epithelium with underlying inflammation. Small mucous cysts are seen in the colon and sometimes ulcers. In the nervous system there may be chromatolysis of ganglion cells, and in some cases patchy demyelination in the spinal cord.

Clinical Features. GENERAL. Pellagra can develop in only six to eight weeks on diets very deficient in niacin and tryptophan. The patient is often underweight, and presents the general features of poor nutrition. There may be amenorrhoea. Pellagra has been called the disease of the three Ds: dermatitis, diarrhoea and dementia.

SKIN. The diagnosis is generally first suggested by the appearance of the skin. Characteristically, there is an erythema resembling severe sunburn, appearing symmetrically over the parts of the body exposed to sunlight, especially the backs of the hands, the wrists and forearms, face and neck. On the neck the lesions characteristically have a V-shape in front, determined by the open top of the shirt or dress and extend round the sides of the neck. This is called Casal's collar or necklace. Local trauma or irritation of the skin may also determine the site of the lesion. The affected areas are well demarcated from normal skin. They are at first red and slightly swollen; they may itch and burn.

In acute cases the skin lesions may progress to vesiculation, cracking, exudation and crusting with ulceration and sometimes secondary infection; but in chronic cases the dermatitis occurs as a roughening and thickening of the skin with dryness, scaling and a brown pigmentation. Dermatitis of the vulva, perineum and perianal area are usually present. Nasolabial dyssebacea is sometimes seen on the face.

DIGESTIVE SYSTEM. Complaints of digestive upset are usual, and diarrhoea is common but not always present. There may be anorexia, nausea, dysphagia, dyspepsia and achlorhydria. The tongue characteristically has a 'raw beef' appearance—red, swollen and painful. Glossitis is an early symptom and may precede the skin lesions. The mouth is sore and often shows angular stomatitis and cheilosis (p. 162). It is probable that a non-infective inflammation extends throughout the gastrointestinal tract and accounts for the diarrhoea; certainly the rectum and anus are frequently inflamed. The diarrhoea is characteristically profuse and watery, sometimes with blood and mucus in the stools.

NERVOUS SYSTEM. In the milder cases the symptoms consist chiefly of weakness, anxiety, depression, irritability and failure of concentration; in severe cases delirium is the most common mental disturbance in the acute form of the disease and dementia in the chronic form. Because of these changes, chronic pellagrins may be admitted to mental hospitals. In chronic cases there may be signs of degenerative changes in the posterior and lateral columns of the spinal cord.

disorientation of time and place, usually
= hallucination and illusion

End state irreversible
state.

Diagnosis. The classical case in an endemic area should present no diagnostic difficulties if a careful dietary and social history is taken and the typical clinical signs are present. The skin lesions are of particular diagnostic importance since they are found only in pellagra, whereas the gastrointestinal and mental features may be present in many other diseases. It is the occasional case in a non-maize eater that may present difficulties. A variety of erythemas and exfoliative skin lesions may mimic pellagra. A nutritional glossitis identical with the tongue changes seen in pellagra may occur without the other signs of the disease. Pellagra may closely resemble sprue and, if the skin changes are minimal, the distinction between the diseases may be difficult.

Pellagra may sometimes occur without any apparent involvement of the skin if the patient has been confined indoors. Such patients may present with neurological manifestations. Glossitis or perineal lesions are usually to be found. This variety is sometimes called 'pellagra sine pellagra' and should be remembered if unexplained delirium or dementia is found in a person who has been taking a poor diet for a prolonged period.

Treatment. SPECIFIC VITAMIN THERAPY. For quick relief of symptoms nicotinamide is given. A suitable dose is 100 mg every four to six hours by mouth, although a smaller dose is likely to be effective. The vitamin is rapidly absorbed from the stomach, despite severe digestive disorders. There is therefore no indication for giving it parenterally. The immediate response to nicotinamide is usually dramatic; within 24 hours the erythema of the skin diminishes, the tongue becomes paler and less painful and the diarrhoea ceases. Often there is also striking improvement in the patient's behaviour and mental attitude.

Nicotinamide alone is usually insufficient to restore health. Some of the features found in pellagra are clearly the result of associated nutritional deficiencies. First, a relatively low intake of protein and the amino acid tryptophan is an essential condition for development of the disease, and hypoalbuminaemia is common. Secondly, anaemia may coexist, either of iron or folate deficiency type. Thirdly, deficiencies of other B complex vitamins are to be expected. Peripheral neuropathy may be caused by thiamin or pyridoxine deficiency, nasolabial dyssebacea and angular stomatitis by riboflavin deficiency and spinal cord lesions, when present, by vitamin B_{12} deficiency. Lastly the patient has usually lost weight, i.e. he has been in a negative calorie balance. Nicotinamide treatment should therefore be supplemented with a nutritious diet, high in protein. Vitamin B complex tablets should be given routinely and iron, folic acid and vitamin B_{12} may be necessary in addition for some cases.

DIET. If possible, the food should provide 100-150 g of high-quality protein, supplied by milk, eggs, meat or fish. Plenty of carbohydrate and fat is also desirable, sufficient to provide up to 3,500 kcal/day, to restore the patient to normal weight. Fruit juice should be given daily. The diet may be poorly tolerated at first, because the mental state of the patient and the sore mouth may make eating difficult. Alcohol must be forbidden.

GENERAL MEASURES. Rest in bed and sedation are necessary for severely ill pellagrins, especially those with marked mental symptoms; they are often troublesome patients, so their behaviour must be tolerated with objective understanding of its cause. If the dermatitis is associated with much crusting or secondary infection, gentle washing with a bland solution is indicated. If the diarrhoea is severe enough to interfere with sleep or to cause electrolyte disturbances, treatment with tincture of opium should be given until it is brought under control with nicotinamide.

Prognosis. In the endemic areas the majority of cases are mild, improving in the winter and relapsing with the increased sunshine in the spring. In long-standing cases there may be persistent mental, spinal cord and digestive disorders.

Occasionally a fulminating form develops, with fever and severe prostration which may be fatal. In the past, most of the deaths arose from secondary infections, notably tuberculosis and dysentery, or from emaciation due to general dietary failure, intensified by the diarrhoea.

Prevention. The remarkable fact that pellagra has vanished from the southern states of America, whereas before the Second World War it afflicted tens of thousands of poor country folk, demonstrates in a dramatic way that the disease is preventable. Its disappearance has sometimes been attributed to the fortification of bread and maize meal with nicotinic acid, but this is only one of several factors which have produced this satisfactory result. The most likely reason is the general improvement in the economic state, education and nutrition of the population.

In Central America the peasants eat a staple diet of maize but pellagra is unusual. The reason is because of the traditional method of boiling the maize in lime water (dilute calcium hydroxide) before they make tortillas. It has been found that the indigestible niacytin is hydrolysed to free niacin in dilute alkali.

Pilot schemes for enrichment of maize meal with nicotinamide and riboflavin in South Africa have been reported recently.

From the standpoint of agricultural policy, it is clearly wise to avoid too much dependence on a single cereal crop, such as maize, or to devote too great an acreage of fertile land to the cultivation of cash-crops, such as cotton or tobacco. Animal husbandry should be encouraged in all areas where pellagra is endemic so that the production of milk and milk products and meat is increased.

For the medical practitioner in such an area, without direct influence in matters of agricultural policy, the best advice that he can give to his patients is to take as much milk, eggs and meat as they can afford. He will also do well to prescribe yeast extract for the families of his pellagrous patients.

RIBOFLAVIN

Chemistry and Physiological Action. Riboflavin is a constituent of the flavoproteins which are concerned with tissue oxidation. It is slightly soluble in water but not in fats. Though stable to boiling in acid solution, in alkaline solution it is decomposed by heat. It is also destroyed by exposure to light.

Dietary Sources. The best sources of riboflavin are liver, kidney, meat, cheese and eggs. Milk and green vegetables contain moderate amounts. It differs from other components of the vitamin B complex in that it occurs in good amounts in dairy produce, but is relatively lacking in cereal grains, especially when highly milled. It is also present in beer. Ordinary methods of cooking do not destroy the vitamin apart from losses that occur when the water in which vegetables have been boiled is discarded. If foods, especially milk, are left exposed to sunshine, large losses may occur. Marmite and Bovril are particularly rich sources of the natural vitamin.

Disorders due to Riboflavin Deficiency

When human volunteers have been given diets very low in riboflavin, the most consistent clinical manifestations have been angular stomatitis, cheilosis and nasolabial seborrhoea; these responded to the addition of pure riboflavin to the deficient diet.

Angular Stomatitis. This is not specific for riboflavin deficiency. Deficiencies of niacin, pyridoxine and iron can all produce it. It can follow herpes febrilis at the angle of the mouth. In Britain the commonest cause is ill-fitting dentures, associated with candidiasis.

Cheilosis. Cheilosis is the name given to a zone of red, denuded epithelium at the line of closure of the lips. It has occurred in experimental pure niacin deficiency. It is often associated with angular stomatitis and frequently seen in pellagrins. It is more commonly seen in ill patients who have been dehydrated and may resemble chapped lips in healthy people who have been exposed to cold winds or excessive sunlight.

Nasolabial Seborrhoea or Dyssebacea. This is the term given to the appearance of enlarged follicles around the sides of the nose which are plugged with dry sebaceous material. This skin change is seen in some patients with pellagra.

Other Abnormalities. Other abnormalities which have been attributed to riboflavin deficiency are vascularisation of the cornea, scrotal dermatitis, a magenta-coloured tongue and anaemia. The place of riboflavin in their causation in man is controversial.

Riboflavin clearly plays a vital role in cellular oxidation and there are communities and individuals who have both minimal dietary intakes and very low concentrations in urine or blood. Yet it is surprising that the clinical effects of riboflavin deficiency are trivial and mostly non-specific. Features of riboflavin deficiency are most likely to be found in pellagrins and in malnourished rice-eaters in S.E. Asia. In the first situation they are overshadowed by niacin deficiency and in the second by thiamin or protein deficiency.

Treatment. The therapeutic dose of riboflavin is 5 mg three times a day by mouth. It gives the patient's urine a green fluorescence. For reasons discussed above, other B complex vitamins should also be given.

PYRIDOXINE

(VITAMIN B_6)

Chemistry and Physiological Action. Vitamin B_6 is not a single substance but consists of three closely related chemical compounds with similar physiological actions. The biologically active form of the vitamin is pyridoxal phosphate, the coenzyme for aminotransferases (transaminases) which play a decisive part in the metabolism of amino acids.

Dietary Sources. Vitamin B_6 is widely distributed both in plants and animal tissues which reflects its importance in the metabolism of many kinds of cell. Meat, liver, pulses, egg yolk, vegetables and the outer 'coats' (bran) of cereal grains are all good sources. The normal adult requirement is 2 mg per day.

Disorders due to Pyridoxine Deficiency

Although pyridoxine plays an important role in the metabolism of amino acids, and although a series of pathological changes in the skin, liver, blood vessels, nervous tissue and bone marrow have been produced experimentally in various animals, disorders due to deficiency of pyridoxine rarely occur in man, and then very seldom as a result of dietary deficiency.

Convulsions, which respond to pyridoxine, have been reported to occur in infants on artificial feeds of powdered milk deficient in pyridoxine. In adults dermatitis, cheilosis, glossitis and angular stomatitis have been produced by means of the pyridoxine inhibitor, 4-desoxy-pyridoxine. The peripheral neuritis associated with isoniazid therapy is due to a conditioned pyridoxine deficiency.

Pyridoxal phosphate is a necessary coenzyme for haem synthesis. A small number of well-documented cases of hypochromic anaemia have been reported which were refractory to treatment with iron given orally or parenterally, but which responded dramatically to the oral administration of 20 to 100 mg of pyridoxine hydrochloride daily. In contrast to the classical case of iron deficiency anaemia, the level of serum iron is normal or high and there is a great increase in stainable iron (sideroblastic anaemia, p. 727). The diagnosis is established by excluding other types of anaemia with high levels of iron in the serum and tissues, e.g. the haemolytic anaemias and especially thalassaemia, and by the therapeutic response to pyridoxine. The mechanism of production of the naturally occurring pyridoxine deficiency anaemia in man is not understood. Neither dietary deficiency nor malabsorption was present in most of the reported cases. Presumably some defect in the intermediary metabolism of pyridoxine is responsible.

Biochemical features of pyridoxine deficiency can occur in women taking oral contraceptives, and it has been reported that the mild depression which affects a small proportion of women on 'the pill' may be relieved by pyridoxine.

VITAMIN B_{12}

(THE COBALAMINS)

Vitamin B_{12} is the name given to a group of cobalamins present only in foodstuffs of animal origin and in micro-organisms—bacteria and moulds—which alone seem capable of synthesising them and are probably the original source. Vitamin B_{12} is the largest molecule essential for human nutrition (molecular weight about 1,350). Its absorption, which occurs in the ileum, is very poor unless gastric intrinsic factor is available. Healthy adults have body stores of about 3,000 μg. The normal requirement is about 2 μg per day. Consequently it takes several years before deficiency becomes manifest when ingestion or absorption of the vitamin ceases.

Physiological Action. Deficiency of vitamin B_{12} affects DNA synthesis so it is most severely felt in tissues where the cells are normally dividing rapidly, e.g. in the blood-forming tissues of the bone marrow and in the gastrointestinal tract. The nervous system is affected by a different biochemical mechanism (p. 166).

Disorders due to Vitamin B_{12} Deficiency

These disorders may rarely result from a strict vegetarian diet, but more commonly from lack of gastric intrinsic factor, either in Addisonian pernicious anaemia (p. 728) or after gastrectomy. They may also occur in intestinal diseases, especially the blind loop syndrome (p. 494) or when there is disease of the ileum. The two principal effects of deficiency are megaloblastic anaemia (p. 727) and subacute combined degeneration of the spinal cord (pp. 168 and 894). A subnormal serum vitamin B_{12} is valuable in making the diagnosis.

FOLATE

Dietary Sources. Fresh, dark-green vegetables, liver and kidney are the best sources, with other green vegetables, pulses, nuts and some seafoods the next best. Beef, fresh fruits, root vegetables and wheaten flour contain a little, whilst milk, eggs and other meats are poor in folic acid. Considerable losses occur when vegetables are boiled for a long time in large amounts of water.

Disorders due to Folate Deficiency

Deficiency of folate leads to megaloblastic anaemia and atrophic changes in parts of the gastrointestinal tract, e.g. the tongue, because folate derivatives are coenzymes for DNA synthesis.

Compared to the rarity of megaloblastic anaemias due to dietary deficiency of vitamin B_{12} in Britain, those due to an inadequate intake of folate are quite common and can develop in 135 days. They are especially likely to occur in pregnancy and in infancy when requirements are increased. Conditioned deficiencies can occur in haemolytic diseases, are frequent in the malabsorption syndrome and are a complication of long-term anti-convulsant therapy for epilepsy (p. 831).

In treatment a daily dose of 5-10 mg of folic acid by mouth is sufficient. It must never be given in Addisonian or other B_{12} deficiency anaemias because it can aggravate or precipitate the neurological features of vitamin B_{12} deficiency.

NUTRITIONAL ANAEMIAS

The life of a red blood corpuscle is about 120 days. The bone marrow is continually making replacements at a rate which enables the total red cell population to be renewed every three to four months. This renewal requires the daily synthesis of 7 to 10 g of haemoglobin and the construction of the corpuscles to carry it. For this synthesis a variety of materials is needed by the bone marrow, particularly certain minerals (especially iron and also copper and cobalt in very small amounts), vitamins (vitamin B_{12}, folate, ascorbic acid, pyridoxine) and protein for the red cell stroma and for globin synthesis. Since these materials must be obtained from food, nutritional anaemias are common wherever the diet is unsatisfactory or when additional demands for nutrients have to be met. The nutritional hypochromic and megaloblastic anaemias are discussed on pages 722 and 731.

Anaemia due to Undernutrition and Starvation

Patients who have lost weight from a simple insufficiency of food are often mildly anaemic. One effect of weight loss from lack of calories is a smaller red cell population in a normal plasma volume. If the patient has lost 25 per cent of his normal lean body weight, the haemoglobin concentration in his blood is likely to be 75 per cent of normal.

Nutritional Anaemia in Tropical Countries

Anaemia, especially the type due to iron deficiency, is common and causes much ill-health and loss of working capacity in all temperate climates even when the economic state of the people is good. In developing tropical countries nutritional anaemias occur even more frequently and are more severe in degree. The basic causes of the different types of anaemia in tropical countries, their clinical features and their treatment, are similar to those in temperate climates (p. 720). There are, however, additional factors which require consideration. The demands for iron may be greatly increased by blood loss in the faeces due to hookworms. In addition significant amounts of iron may be lost in the sweat and shed skin cells in hot climates. When these additional factors operate in persons who are already partaking of diets which may be lacking in iron and protein, it is not surprising that iron deficiency anaemia is frequent and severe in tropical countries.

The nutritional megaloblastic anaemias of tropical climates are associated with predominantly carbohydrate diets poor in animal protein and hence low in vitamin B_{12} and especially in folate. The role of protein malnutrition in tropical nutritional anaemia has been extensively studied in kwashiorkor (p. 118). This anaemia is usually moderate in degree and is normocytic or slightly macrocytic with a normoblastic bone marrow. However, when parasitic infections are present, when there is liver disease or when the intake of haematinics such as iron, folate and vitamin B_{12} is poor, the resultant anaemia in kwashiorkor may be severe and may be of hypochromic, megaloblastic or mixed type, giving a dimorphic peripheral blood picture. For further information about anaemia in the tropics the reader is referred to the Tropical Diseases Supplement.

NUTRITIONAL NEUROLOGICAL SYNDROMES

The nervous system is susceptible to damage from dietary causes. This is scarcely surprising since the nutritional welfare of this system is dependent on finely adjusted mechanisms requiring a source of energy derived only from carbohydrate of which it has no immediate store, and a variety of highly complicated enzyme systems which govern and control the use of this energy.

The various nutritional neuropathies arise only when there is either a gross defect in the quality or quantity of the food or a digestive disturbance leading to failure of absorption. They are mostly chronic conditions and present a strong contrast to the clinical features of other nutritional disorders, such as the heart failure of wet beriberi and the haemorrhagic manifestations of scurvy, which usually respond dramatically to treatment with the appropriate vitamin. Nerve cells, however, have limited powers of recovery compared with other cells; hence no sudden or striking diminution of symptoms or signs in any chronic disease of the nervous system with structural changes can be expected to follow dietary or vitamin therapy.

Classification

1. The lesion is predominantly in the peripheral nerves in:
   - (*a*) The polyneuropathies of beriberi, alcoholism, and pregnancy.
   - (*b*) The burning feet syndrome.
2. The lesion is predominantly in the central nervous system in:
   - (*a*) The cord syndromes:
     - (i) vitamin B_{12} neuropathy (subacute degeneration of the cord);
     - (ii) tropical ataxic neuropathy;
     - (iii) lathyrism and other causes of spastic paraplegia.
   - (*b*) Nutritional amblyopia.
   - (*c*) Wernicke's encephalopathy (p. 896).

Nutritional and Alcoholic Polyneuropathies

The polyneuropathy of dry Oriental beriberi is the classic example. It arises from the consumption of a poor diet composed chiefly of polished rice, but is not due to lack of any one single dietary nutrient. Nutritional neuropathies occur most frequently in thin, underfed people. In countries outside the tropics an essentially similar disease occurs not infrequently in chronic alcoholics and rarely during pregnancy when vomiting is a prominent feature, and in the malabsorption syndrome.

Thiamin deficiency is clearly important in the pathogenesis of both Oriental and alcoholic polyneuropathy. However, polyneuropathy can be produced in man by deficiency of pyridoxine, pantothenic acid, vitamin B_{12} and probably niacin. In different clinical situations one or more of these may have been associated. Biochemical tests on the blood when the patient is seen do not necessarily reflect the nutritional status of the peripheral nerves when the process started. It should be borne in mind too that toxins can produce a similar picture and isoniazid is more likely to cause neuropathy in malnourished people because it antagonises the action of pyridoxine (p. 163).

The morbid anatomy and clinical features are similar to those of the polyneuropathy of dry beriberi (p. 155). For further information about disorders of the peripheral nerves see page 899.

Treatment. This demands, first, attention to the patient's diet both in quantity and quality. The neurological lesions will not improve until the patient regains his strength, so every effort should be made to restore him to his original body weight. Plenty of protein—milk, eggs, meat, fish—is desirable, supplemented by generous doses of the vitamin B complex. If these are given as tablets care must be taken that all the vitamins are included. Some authorities prefer natural sources such as yeast or yeast extract (e.g. Marmite), rice bran or wheat germ. If the patient has anorexia, vomiting or malabsorption the vitamin B complex should be given by injection. Physiotherapy is very important and may need to be prolonged.

Burning Feet Syndrome

Outbreaks of this clinical syndrome have occurred in Europe, Central America, Africa and India among people living on very poor diets. It became very troublesome among European prisoners in the Far East during the Second World War.

The syndrome usually results from the prolonged consumption of a diet deficient in the B group of vitamins. Patients who suffer from it may also develop mucocutaneous signs suggesting riboflavin deficiency (p. 162) or nutritional amblyopia (p. 169), but rarely frank beriberi.

The earliest symptom is aching, burning or throbbing in the feet. This becomes more intense and is followed by sharp, stabbing, shooting pains, which may spread up as far as the knee like an electric shock, causing excruciating agony. They come on in paroxysms and are usually worse at night. Objective signs of neuropathy are seldom marked unless the polyneuropathy of beriberi co-exists. The tendon jerks are usually normal but may be exaggerated. In the great majority of cases there is no demonstrable sensory change.

The therapeutic response to pure vitamin preparations has been variable. Some patients have responded to pantothenic acid preparations, some to riboflavin or other B complex vitamins, some not to any combination of vitamins.

Vitamin B_{12} Neuropathy

(SUBACUTE COMBINED DEGENERATION OF THE CORD)

Dysfunction or degeneration of the posterior and lateral colums of the spinal cord together with peripheral neuropathy usually occurs in association with Addisonian pernicious anaemia (p. 728). Less commonly it occurs after gastrectomy or in other causes of vitamin B_{12} malabsorption (p. 495). Rarely it arises from a lack of vitamin B_{12} in the diet, e.g. in some castes of strict Hindu and in vegans (vegetarians who eat no animal products of any kind). There may be little anaemia presumably because a vegetable diet supplies sufficient folic acid, which can correct vitamin B_{12} deficiency megaloblastic anaemia but not the neuropathy. Serum vitamin B_{12} is subnormal. The clinical features and treatment are discussed on pages 894 to 896.

Tropical Ataxic Neuropathy

Patients have been reported from Jamaica, Nigeria and East Africa with signs indicating a lesion in the posterior columns of the spinal cord. The gait is unsteady, Romberg's test (p. 805) is positive and vibration sense in the legs is often lost. There may be associated amblyopia or deafness.

Although these patients have been eating a poor diet, and are often thin and may have muco-cutaneous signs of vitamin deficiency, recent investigations suggest that the probable cause is chronic cyanide ingestion from prolonged large intakes of certain foods, particularly cassava. Patients have been found to have high thiocyanate concentrations in their blood. Traditional methods of cooking, if properly followed, wash or boil off most of the cyanide in cassava.

Patients may be expected to improve if changed to a balanced diet and vitamin B_{12} may help in detoxifying the cyanide in the body.

Spastic Paraplegia

Lathyrism. *Lathyrus sativus* is a drought-resistant pulse, widely grown in parts of India. If eaten in excessive amounts, it gives rise to lathyrism, a nutritional spastic paraplegia.

Epidemic lathyrism is associated with undernutrition since the pulse is eaten in large quantities only when the main crops have failed. If, because of drought, there is a poor crop of wheat, a useful harvest of lathyrus may be reaped. Eaten in small quantities, lathyrus seeds are a valuable food. But if they are the main source of energy, disease of the spinal cord may result. A neurotoxin has recently been isolated from lathyrus seeds, β-N-oxalyl-amino-L-alanine (BOAA).

The onset of paralysis is usually sudden and is often preceded by exertion or exposure to cold. The condition is a spastic paralysis of the lower limbs, due to a localised lesion of the lower parts of the pyramidal tracts. The motor nerves to the muscles of the trunk, upper limbs and sphincters are spared. The sensory nervous system is not involved. In severe cases the disease progresses to a paraplegia in flexion, but in mild cases there is only stiffness and weakness of the legs and exaggerated knee and ankle jerks.

There is no specific treatment. All patients need a good diet. Minor cases may make a complete recovery following satisfactory dietary and physical rehabilitation. In most cases the pathological changes are irreversible and the patients drift into beggary and become an important social problem.

Other Forms of Spastic Paraplegia. Spastic paraplegia of uncertain origin occurring in adults is not infrequently seen in various parts of Asia and Africa and in Jamaica. Toxins in plant foods or 'bush teas' have been suspected.

On the Pacific island of Guam there is an exceptionally high incidence of amyotrophic lateral sclerosis (p. 882). It is likely that this results from the indigenous population's regular consumption of cycad seeds.

Nutritional Amblyopia

A progressive failure of vision attributable to a retrobulbar neuropathy occurred amongst prisoners-of-war in the Far East in the Second World War. Similar amblyopias occasionally occur in beriberi, pellagra and subacute combined degeneration of the spinal cord. Cases have been reported in Nigeria and Jamaica. The patients appear to have had one feature in common, a period of months on diets grossly deficient in respect of many essential nutrients. A similar condition occurs in affluent communities in some heavy tobacco smokers (p. 815).

A typical history is that in over a period of three weeks or so there is a growing inability to see the colours of small objects. A mist obscures the central field of vision and gradually becomes so intense that it becomes impossible to recognise acquaintances. There is usually no pain. On examination of the visual fields a central or paracentral scotoma is present. The visual acuity varies greatly. On ophthalmoscopy there is temporal pallor of the optic discs in severe cases.

Most cases in the far East responded to a good diet supplemented by some natural source of the entire vitamin B complex. When vision is markedly affected little improvement results from any form of treatment.

NUTRITIONAL DISORDERS OF THE SKIN, HAIR, NAILS, MOUTH AND EYES

Follicular keratosis (p. 135), folliculosis (p. 149), xeroderma (dryness of the skin, crackled skin, crazy paving skin), pachyderma (elephant skin), atrophy of the skin, pigmentary changes of the skin and tropical ulcers are disorders of the skin and mucous membranes which are frequently seen in persons subsisting for long periods on unsatisfactory diets. In such individuals there may also be changes in the texture and colour of the hair (p. 119), and the finger nails may be thin, brittle or spoon-shaped (p. 722). Disorders of the eye may also be present (p. 133), and deficiency of nicotinic acid, riboflavin, vitamin B_{12}, folate or iron may give rise to a nutritional glossitis and stomatitis. Until more is known about the chemical pathology of the skin, hair, nails and eyes it will continue to be difficult to assess the significance of certain clinical changes in these structures which are not infrequently seen in examination of underfed or malnourished people. Hence it would be unwise always to attribute these disorders solely to dietary deficiency. Undoubtedly exposure to dirt, heat, moisture, trauma and infection can contribute to their causation. The practical importance of these stigmata is that their presence in either an individual or a community should at once draw attention to the diet.

BIOCHEMICAL DIAGNOSIS AND SUBCLINICAL VITAMIN DEFICIENCIES

Biochemical methods are an integral part of modern medical diagnosis. For example, plasma sodium and potassium concentrations are essential for the diagnosis and treatment of difficult electrolyte problems and serum or red cell folate and serum vitamin B_{12} concentrations are desirable before treating a patient with megaloblastic anaemia. Likewise with the other vitamins, biochemical tests have been developed in recent years which are more or less valuable:

(*a*) for confirming the diagnosis of a deficiency disease in places where it is uncommonly seen or if the clinical picture is complicated.
(*b*) in community surveys, for identifying individuals with subclinical vitamin deficiencies.

The tests which can be used for the major vitamins are listed in Table 2. As with other tests in chemical pathology there can be false positives and false negatives. Each result needs to be evaluated with critical understanding; for example, serum vitamin B_{12} is increased in acute hepatitis and alkaline phosphatase may not be elevated if rickets is accompanied by PCM.

In general when the dietary intake of a nutrient is inadequate the results in the individual go through three stages. The first stage is that of adaptation to the low intake. For example, urine excretion falls but there is no evidence of abnormal function or of depletion of the cells.

TABLE 2

Biochemical Methods for Diagnosing Nutritional Status

Nutrient	Principal Methods		Supplementary Methods
	(A) Indicating Reduced Intake	(B) Indicating Impaired Function (IF) or Cell Depletion (CD)	
Protein	Urinary nitrogen	SERUM ALBUMIN (IF)	Fasting plasma amino acid pattern
Vitamin A	PLASMA VITAMIN A (retinol) and PLASMA CAROTENE		
Thiamin	Urinary thiamin	RBC TRANSKETOLASE and TPP EFFECT (IF)	Plasma pyruvate and lactate
Riboflavin	Urinary riboflavin	RBC glutathione reductase and FAD effect (IF)	RBC riboflavin
Niacin	URINE N'METHYL NICOTINAMIDE and 2-pyridone		Fasting plasma tryptophan
Pyridoxine	Urinary 4-pyridoxic acid	RBC glutamic oxal-acetic transaminase and PP effect (IF)	Urinary xanthurenic acid after tryptophan load
Folic Acid	Serum folate (*Lactobacillus casei*)	RED CELL FOLATE (CD) Haemoglobin, PCV and smear (IF)	Urinary FIGLU after histidine load. Bone marrow morphology
Vitamin B_{12}	SERUM VITAMIN B_{12} (*Euglena gracilis*)	Haemoglobin, PCV and smear (IF)	Schilling test. Bone marrow morphology
Ascorbic Acid	Serum ascorbic acid	LEUCOCYTE ASCORBIC ACID (CD)	Urinary ascorbic acid
Vitamin D	(Serum 25 hydroxy-cholecalciferol)	SERUM ALKALINE PHOSPHATASE (IF)	Serum calcium and inorganic phosphorus

(The tests in Capital letters are those most commonly used at present.)

In the second stage there are in addition biochemical changes indicating either impaired function, e.g. reduced red cell transketolase activity in thiamin deficiency, or cellular depletion, e.g. reduced white cell ascorbic acid. But clinical manifestations of deficiency are absent or non-specific.

The third stage is that of clinical deficiency disease.

Most clinical biochemistry laboratories provide only some of the methods as a routine but others might be provided if there was a good reason or, alternatively, specimens could be sent to a laboratory specialising in nutrition research.

PREVENTION OF NUTRITIONAL DEFICIENCIES

The medical profession can do little, directly, towards preventing nutritional disorders. The economic, social and agricultural issues involved are primarily the concern of statesmen, administrators and farmers. In addition, effective national programmes of population control must be evolved in many countries.

The problem of the present world shortage of calories is unlikely to be improved except by international action, involving the proper agricultural development of fertile, but at present unproductive, parts of the world and by effective family planning.

At the national level, individual countries that are short of food can do much towards making the best use of their limited supplies by ensuring the equitable distribution of essential foodstuffs and by preventing black market operations. In Britain, since 1940, there has been a great achievement in making special provision for 'vulnerable groups' (mothers and children). School meals, school milk, a guaranteed milk supply and supplements of cod-liver oil and orange juice for these groups are, without doubt, a most important contribution to the present and future health of the country. Since osteomalacia and minor degrees of scurvy are now known to be more common in old people than was formerly recognised, especially if they are living alone and are confined to the house by infirmity, it is suggested that they should be classified as a 'vulnerable group' and that a free supplement of cod-liver oil and orange juice should be provided by the National Health Service. The fortification of foods, such as the addition of calcium carbonate to bread and of fat-soluble vitamins to margarine, is also a nation-wide contribution to better nutrition. The development of proper Maternity and Child Welfare Services provides a means for better education in sound nutrition.

At the community level, the individual doctor has a chance to help by giving advice to the housewife on what foods to select and how to make the best use of them. In a more general way, doctors have an important responsibility in keeping their patients properly informed about the importance to health of good nutrition. The food policies of the future can be influenced decisively for good, if those responsible for them acquire a proper understanding of the medical problems involved.

A. S. TRUSWELL.
F. J. WRIGHT.

OBESITY

Obesity is the most common nutritional disorder in infants, children and adults in affluent societies, where it is responsible for more ill-health than all the vitamin deficiencies put together.

The importance of obesity requires constant emphasis, not only because of the excess mortality it carries, but also because of numerous complications, and the predisposition it creates to common and potentially serious conditions such as diabetes mellitus. It reduces the efficiency of those affected, it detracts from their ability to participate in many normal activities, and it is frequently associated with emotional and other psychological disturbances, all of which may interfere in a major way with the welfare of an individual, a family, or a community.

Epidemiology. Although a large proportion of the population of many communities is overweight by the standards to be described, and in spite of this often appear to be free of any handicap attributable to obesity, the condition is a morbid state, and therefore one that merits close attention.

Many of the factors bearing on the prevalence of the disorder will be discussed later, but there are others of importance to be summarised here. Genetic and racial components predisposing to obesity are certainly important: the geographical, climatic, occupational and the rural or urban nature of the environment help also to determine the prevalence and severity of the disability. Dietetic traditions and habits, the opportunities provided by increasing affluence, the diminishing need for hard physical work, and even the trends of fashion must also be taken into account when comparisons are made between individuals or groups for clinical or epidemiological purposes.

Definition and Standards. Obesity can be defined as an abnormal accumulation of fat in the stores of adipose tissue throughout the body. Recognising that these stores tend to increase with age in adult life, and to diminish again after the sixth decade, most tables published as guides quote figures for normal weight at specified heights for adult men and women in successive age-groups. While this may be realistic, the concept of an inevitable and apparently physiological increase in weight in middle age may be neither correct nor in the best interests of patients in this age-group. A more effective guide for therapeutic advice is based therefore on the notion of an ideal or desirable weight to be maintained at any age beyond early adult life, and such a table is provided on page 1007. Statistics based on average weights may seem to condone an inappropriate increase in weight. A suitable working rule for the treatment of obesity therefore is that patients should remain within 10 per cent of the desirable weight for any given height.

A useful additional standard for the assessment of overweight is available in the measurement of skinfold thickness, which includes a layer of subcutaneous fat. Special springloaded 'Harpenden' callipers are available for this purpose. The measurement is most reliable when made over the triceps muscle. Obesity is indicated by readings above 20 mm in a man and above 28 mm in a woman.

Aetiology. FAT DEPOT SIZE. Adipose tissue can be regarded as a collection of cells which are larger or smaller depending on their content of fat. Thus two major variables can be recognised, namely the number of cells, and the size of the cells, depending on the amount of fat in each. Overfeeding in the first year of life appears to be followed by an abnormal proliferation of fat cells:

these can be modified in size by depletion or increase of their content of fat, but the capacity of the adipose tissue to accumulate fat is never reduced and persists in the form of an excessive number of cells.

SEX. The normal fat content of young adult women, approximately 15 per cent of body weight, is about twice that of young men. With advancing years, women are more prone to obesity than men. The gain in weight which usually occurs in pregnancy may not be corrected in the months after delivery, especially since breast feeding is so unfashionable. In addition, gain in weight at and after the menopause frequently aggravates a disability established in earlier years.

GENETIC AND ENVIRONMENTAL FACTORS. While the incidence of obesity is affected by many other factors, inheritance also plays an important role. Investigation has shown that in addition to the contribution of environmental considerations such as the dietary habits of the family, economic factors, and exercise, or lack of it, a genetic component can be identified in many cases, though this is far from universal; its mode of transmission and operation is still not clear.

ENDOCRINE AND METABOLIC FACTORS. Many obese patients find it difficult to accept that the principles of conservation and expenditure of energy apply equally to themselves as to the non-obese. Frequently they are convinced that they gain weight inordinately on an intake of food and drink that can be taken with impunity by their non-obese peers. They argue that their failure to lose weight, while restricting their intake of food, must have an explanation in either a glandular or a metabolic disorder which would account for the apparent breach of the laws of thermodynamics. It has to be assumed, albeit cautiously, that while patients may not deliberately attempt to mislead the physician, they can be expected to present the facts about their dietary habits in the light most favourable to themselves, so that in most circumstances their estimates are likely to be of little more than anecdotal value.

Endocrine disorders may contribute in a minor way to a patient's difficulties in maintaining a normal weight. For example, in Cushing's syndrome (p. 656), adrenocortical hyperfunction is often associated with a gain in weight and an increase in body fat, mainly confined to the head, neck and trunk, but sparing the limbs. In pregnancy, endocrine factors contribute to the increase in weight. In hypothyroidism, diminished energy expenditure may be associated with gain in weight. These endocrine variables, however, are certainly unimportant or irrelevant for most obese patients.

The association of obesity and diabetes mellitus is well recognised and is particularly important because of the increased morbidity and mortality that these two conditions carry. It applies mainly in the older group of diabetic patients, with adult or maturity-onset diabetes. Obesity is associated with increased insulin secretion and with increased resistance to the action of insulin; both of these are reversible with weight reduction. When diabetes has become manifest in an obese patient, it is sometimes possible to reverse the diabetic biochemical abnormalities by weight reduction alone.

PSYCHOLOGICAL FACTORS. Obese patients are often psychologically disturbed, though it may be difficult to distinguish between cause and effect. Depressed or anxious patients or the emotionally deprived may seek relief in food, while many patients, especially younger adult females, are often greatly ashamed of their appearance. A patient in the latter group is easier to treat than the older patient who has lost any ambition to recover a more youthful appearance. An analogy is sometimes drawn between overeating as an addiction to food, and addiction to alcohol or cigarettes: food, however, is a more fundamental need than either alcohol or tobacco so that the comparison has limited validity, but may be useful in the management of some patients.

APPETITE AND FEEDING PATTERNS. There can be no doubt that people who consume more calories than they require to match their energy output will gain weight. Excellent evidence exists in animal models that damage to hypothalamic centres can lead to obesity, and from this it is sometimes deduced that an imbalance between appetite and satiety centres in the hypothalamus leads to overeating. The interpretation of these experiments in rats, and studies in obese and lean humans have shown that the fat rats and the obese humans share certain differences from their normal counterparts. Both are less responsive than normal to satiety, that is, in knowing when to stop eating, and surprisingly, after deprivation from food, both eat less than normal controls. In this sense they are said to be under-responsive to 'internal cues', in misjudging an appropriate response to their nutritional status. By contrast, with free access to food they over-respond by eating to excess of foods they find particularly palatable, but eat less than normal controls when the food offered is unpalatable. Thus they are said to be hyper-responsive to 'external cues', in this case the attractiveness of the food offered.

Many people develop the habit, sometimes deliberately, of taking one large meal a day, rather than three or more smaller meals. There are grounds for suggesting that such a habit is more likely to be associated with obesity than a more evenly spaced intake of the same amount of food at intervals throughout the day.

PHYSICAL ACTIVITY. It is well recognised that physical activity is less in the obese than in the lean, though the amount of energy expended by an obese person on most tasks is likely to be more because of the extra weight to be moved. There is also evidence to suggest that below a certain level of exercise the relationship between appetite and energy requirement is more difficult to maintain.

Energy expenditure on walking in quite considerable: a normal man walking at 3½ miles per hour would use about 300 calories per hour. In cumulative terms, this amounts to the equivalent of more than 1 kg of adipose tissue per month, by no means a negligible consideration in relation to energy balance.

Social and industrial trends have steadily diminished the need in the developed societies for energy expenditure, and while some maintain their interests and participation in physical recreation, the majority become spectators exclusively at an early age.

SOCIAL AND ECONOMIC FACTORS. Obesity is more prevalent, in most but not all societies, in the lower social grades. The reasons for this are complex, but one important factor is the higher intake of carbohydrate derived from the less expensive foods, which may be associated in turn with relative hyperinsulinism and increased lipogenesis.

ENERGY BALANCE. It has sometimes been suggested that differences between the fat and the lean could be due to inordinately efficient absorption in the obese as compared with those of normal weight, or that the lean have a special mechanism denied to the obese for 'burning off' excess calories ('luxus Konsumption'). Various factors, for example a fat mobilising substance, and an anorexigenic substance produced during exercise have also been postulated and supported by experimental work, to account for the difficulties of the obese in maintaining a normal weight.

COMMENT. No single factor can be held to be responsible for the very common and sometimes serious problem represented by obesity. The simple general conclusion emerges that obesity represents an accumulation of energy in excess of requirements, and that weight reduction can only be achieved by reducing energy intake, by increasing output, or by a combination of the two.

Clinical Features. The diagnosis will be apparent from the patient's appearance and is confirmed by measurement of weight and height. The amount of surplus tissue can be estimated by reference to Table 18 (p. 1007). The distribution of adipose tissue is variable, but measurement of the skin-fold thickness in the arm over the triceps muscle has been found to be a useful indicator (p. 173).

Complications. In addition to aesthetic considerations and psychological repercussions, obesity leads to mechanical disabilities, predisposes to metabolic and cardiovascular disorders and so reduces the expectancy of life.

Mechanical Disability. The human skeleton is not well adapted to carry an extra load; consequently flat feet and osteoarthrosis of the knees, hips and lumbar spine are more common in obese people, who are also less mobile and more accident prone. The abdominal muscles that support the viscera and those in the legs whose contractions promote venous return, are less efficient with consequent abdominal and diaphragmatic hernias and varicose veins. Adipose tissue around the trunk interferes with the mechanics of respiration and predisposes to bronchitis. Chronic infection of the skin occurs between folds of fat under the breasts and in the axillae (intertrigo).

Metabolic. Obesity may be associated with an elevated level of cholesterol and triglyceride in the blood; perhaps in consequence, obese people develop gallstones more frequently than those of normal weight. The association of obesity, diabetes mellitus and atherosclerosis may also be developed through disordered lipid metabolism. Gout afflicts the obese more commonly than others.

Cardiovascular. Apart from atherosclerosis, obese persons suffer from hypertension more commonly than those of normal weight. The work of the heart is increased by the extra mechanical effort needed in moving the overweight body and by an increased peripheral vascular resistance in patients with hypertension.

This, coupled with the tendency to coronary atherosclerosis, accounts for the liability to angina pectoris and cardiac failure among obese people in middle life.

Life Expectancy. Obesity constitutes a poor risk from the stand-point of life insurance. The statistics of the Metropolitan Life Insurance Co. (USA) have shown that men 45 years of age, who are of medium height and frame and weigh 90 kg, which is 16 kg above the average, can expect to live four years less than men of comparable build who weigh 68 kg, which is within the range of desirable weights. The risks of obesity in women are somewhat less.

Diagnosis. This very common disorder is frequently overlooked because the doctor is preoccupied by one of its many complications or simply ignores it because it is so familiar. To weigh the patient and measure his height must be just as much a routine part of clinical examination as taking the blood pressure or testing the urine. People with small frames may appear to be of normal weight as judged by accepted standards, and yet may be obese; their obesity, often concentrated in the abdomen, is easily overlooked. Athletes in training are sometimes considerably overweight as judged by normal standards; their extra weight is due to muscular hypertrophy.

Obesity must be distinguished from a gain in weight due to occult oedema in cardiac failure or renal or hepatic disease. Oedema does not generally become manifest clinically until the extracellular fluid is increased by 10 per cent or more. In hypothyroidism there may be a sufficient accumulation of myxoedematous tissue to cause excessive weight.

Treatment

GENERAL CONSIDERATIONS. Since obesity is so common and produces so few symptoms in its earlier stages, it remains a personal but socially acceptable problem for most patients, scarcely seeming to merit the major effort involved in its correction. For a previously obese person to maintain a normal weight often demands persisting indefinitely with some dietary restrictions, even when the target weight has been attained. The majority of patients are unable or unwilling to sustain the effort required. The very high relapse rate, as much as 80 per cent, among patients who may have reduced their weight appropriately, is a clear indication of the intractable nature of the disability.

The most important single requirement in the management of obesity is education of the patient. The more they can be taught about the nature and behaviour of the problem, the more likely are they to succeed. This makes heavy demands on the time, energy, skill and enthusiasm of the doctors, dietitians, and nurses who are called upon to supervise these patients. Most have already made attempts to reduce their weight either on their own responsibility, or on their doctors' advice, or as frequently happens now, with the support of lay groups run for the express purpose of helping patients to diet, for example 'Weight Watchers', or 'Tops' (Take Off Pounds Sensibly). The number of patients requiring supervision is so great, the need for this support is so prolonged, and the success of some of these lay organisations compares so favourably with conventional medical methods, that until medical treatment has something considerably more effective to offer, it is justifiable to take advantage of the facilities of these groups. Most of these organisations refer members to their own doctors at the first suggestion of any untoward development.

However this supervision is arranged, it is most important for success that these patients should be given precise instructions as to how they should reorganise their dietary and other habits. It is essential also that they should remain under formal care, attending at frequent intervals, certainly of no longer than two weeks at first.

Among the important lessons to be learned by obese patients is the need to manage the disorder themselves. Unlike most conditions for which they seek advice, success does not depend upon operations, drugs, injections or other manipulations undertaken by the therapist, but rather on the ability of the patient to accept advice, to act upon it, and to persist indefinitely with some restrictions on their dietary freedom. Initiative and action in this matter therefore rests with the patient, and the physician's contribution at all times must be seen to be advisory and supportive only. The patient must recognise that he or she will need to modify radically an instinctive urge of lifelong duration if success is to be permanent.

Finally, if rewards can be set for achievements made in weight reduction and maintenance, in addition to the recovery of a more attractive figure, the ability to wear standard-size garments, to take part in swimming and other activities without appearing conspicuous or even ridiculous, the task will seem less formidable and the undertaking so much more worth while.

The basic requirement for the treatment of obesity, whether it occurs in infants, children or adults, is the regulation of the daily intake of energy sources. In the first instance an unweighed diet is used, but if this is not effective, the stricter discipline of a weighed diet may need to be imposed for a time. In some resistant cases anorectic drugs (p. 181) may provide some temporary help. Obese patients who fail to respond to any of these measures require further investigation from both physical and psychological aspects and intensive treatment under strict supervision in hospital.

THE CONSTRUCTION OF A WEIGHT-REDUCING DIET. Energy ouput has been determined with great accuracy for people undertaking various activities. To keep in caloric balance a person doing sedentary clerical work will require about 2,000-2,500 kcal daily, a person doing light work 2,500-3,000 kcal, while a person doing heavy work, such as felling trees, may need 4,000 kcal or even more.

An obese middle-aged housewife will usually lose weight satisfactorily on a diet providing about 1,000 kcal/day, such as Diet No. 4 (p. 988). If her daily energy expenditure is 2,200 kcal the negative balance will be 1,200 kcal/day. The caloric value of obese tissue is about 7·5 kcal/g. The weekly negative caloric balance is therefore equivalent to $\frac{1200 \times 7}{7{\cdot}5}$ g or 1·1 kg (2·4 lb). A weekly weight loss of about 1 kg should be the general aim. An obese man engaged in active physical work cannot tolerate a diet as low as 1,000 kcal/day. A satisfactory weight loss can be expected from a diet containing 1,500-1,600 kcal/day. Diet No. 4 can be used for this purpose by the addition of 3 carbohydrate exchanges, 2 protein exchanges and $\frac{1}{2}$ a fat exchange (p. 993) and by increasing the milk allowance to 1 pint a day.

Protein. The protein content of the diet should be 50-60 g/day which is sufficient to maintain nitrogen balance. Some weight-reducing regimes have been based on the principle of eating mostly meat and other foods rich in protein. Some scientific support was given to this principle by the knowledge that proteins stimulate specific dynamic action and should encourage the dissipation of surplus calories, but this is of little help in the prevention or treatment of obesity. High protein diets may satisfy appetite more effectively than high carbohydrate diets, but they are expensive, they may not be particularly palatable after a time, they may have a high incidental content of fat, and so are seldom practicable.

Carbohydrate. The intake of foods rich in carbohydrate should be drastically reduced since over-indulgence in such foods is commonly associated with obesity. There have been unfounded fears that too drastic reduction of the carbohydrate intake may lead to ketosis and that this ketosis is responsible for numerous complaints such as headache, weakness and nausea, sometimes made by obese patients when first undertaking dietary restrictions. In fact, obese people seldom develop more than a trace of ketosis and never sufficient to cause symptoms as long as they consume small amounts of carbohydrates.

In a diet of 1,000 kcal/day, 100 g of carbohydrate is a suitable allowance.

Fat. A diet containing 100 g of carbohydrate and 50-60 g of protein, cannot include more than 40-45 g of fat. This allowance of fat, though small, is sufficient to make the diet palatable.

It is sometimes suggested that there is no need to restrict the intake of fat in obese patients. Eat fat and get slim is advice which has an obvious appeal. Patients however cannot be expected to tolerate for more than a short time a bizarre diet which is rich in fat and low in carbohydrate and any value this advice may have will be related to the palatability of the diet.

Vitamins. A properly designed reducing diet should contain plenty of green vegetables and fruits, since they contain few calories, while their bulk helps to fill the stomach and relieve hunger; they also help to minimise the constipation common on a low food intake. Their vitamin A and vitamin C activity will be sufficient to meet the body's needs. With meat, fish and eggs in the diet and little or no refined cereals and sugar, it is improbable that deficiency of any component of the vitamin B complex will arise. A good reducing diet will thus meet the patient's needs for vitamins. Any doubt about the vitamin intake of a particular patient may be resolved by prescribing a natural source of the vitamin B complex such as yeast extract (e.g. Marmite) or wheat germ (e.g. Bemax).

Minerals. The only minerals that need serious consideration are calcium and iron. Provided that the diet includes half a pint of skimmed milk, there is little likelihood of a negative calcium balance developing in an adult. The supply of iron is less sure and may call for the prescription of iron supplements. In the treatment of obese patients the doctor must be constantly on the alert for the earliest signs of anaemia.

Water and Salt. At one time patients were often advised to restrict their intake of water, but there is no logical reason for keeping fat patients thirsty. Sweetened 'juices' must be avoided, except those sold for diabetic patients, which have a low caloric content. Alcoholic drinks are also a source of calories and hence are best avoided, but if taken, a corresponding reduction in the diet is necessary.

In addition to liability to the usual causes of oedema, the obese are also particularly susceptible to water and salt retention. Diuretics should be used with discrimination in these patients, because potassium depletion is particularly liable to occur while they are on a reducing regimen, because salt restriction alone may be sufficient to alleviate oedema, and because adherence to a reducing regimen will often relieve the oedema of obesity in any case. When diuretics are considered essential, potassium supplements should also be given.

Proprietary Powdered Food Products. These contain a balanced mixture of protein, carbohydrate and fat with the addition of essential vitamins and minerals but are not recommended for the routine treatment of obesity.

THE UNWEIGHED DIET. With an intelligent co-operative patient who is determined to lose weight and who is only moderately obese all that may be necessary is to discuss in detail the essentials of treatment described above and the kind of foods which must be avoided because of their high calorie content (p. 989). If this is not successful then more detailed instructions are necessary and the patient should be treated with an unweighed but measured diet such as Diet No. 4 (p. 988). No scales are required to weigh the foods as all the household measures needed are incorporated in the instructions. The content of the diet can be varied by making use of the exchanges available for bread or by eating foods of a low calorie content (Group A, p. 989) which can be taken as desired.

Diet No. 4 is, in general, suitable for the treatment of an overweight middle-aged housewife in Britain but it may be unsuitable in other circumstances and in other climates. Dietitians with knowledge of local eating habits can achieve a great deal of good by devising diets suitable to the established customs which provide about 1,000 kcal made up from about 100 g carbohydrate, 50-60 g protein and 40-45 g fat.

Failure to respond to the unweighed diet indicates that the patient requires the stricter regime provided by a weighed diet.

THE WEIGHED DIET. Diet No. 4 (p. 988) is also available as a weighed diet. The patients must weigh what they are about to eat on suitable scales kept for this purpose on the sideboard or in the kitchen. Their use must be continued for some weeks until the doctor is satisfied that the patient can judge quantities of food correctly.

INTENSIVE DIETETIC TREATMENT. The dietetic regimes described above aim at achieving a rate of weight loss of just over 1 kg each week. Very fat patients will have to persist with such a regime for predictable periods before achieving their declared target weight. Slow progress may be disheartening and lead to the abandonment of treatment. Provided there are no orthopaedic or cardiovascular complications, it is possible to increase the physical activities gradually and reduce the diet still further. Patients have been kept on diets providing only 400 kcal/day for periods of several weeks, whilst they walked 10 miles daily. This regime involved negative balances of the order of 3,000 kcal/day. The patients lost weight at rates of up to 3 kg a week yet remained well.

A period of several weeks of starvation in hospital, only water and non-caloric drinks with vitamin and mineral supplements being allowed, has been recommended for very obese patients who have failed to respond to orthodox anti-obesity treatment. Although the initial loss of weight may be marked the long-term results are no more satisfactory than other systems since many patients regain most of the weight lost when this strict regime is discontinued. However, it may be of value for selected patients, particularly as a demonstration of what can be achieved with sufficient discipline. Such a regime is clearly contraindicated for older patients, especially if they have cardiovascular complications, and deaths have occasionally occurred. Ketosis may be troublesome in the early stages, and hyperuricaemia, sometimes accompanied by gout, may occur.

EXERCISE. Most obese patients lead sedentary lives and the full extent to which urban and industrial life restricts activity is only now being realised. There is little doubt that the health of most obese people would be improved by exercise, e.g. walking, swimming, gardening, provided it does not exceed their cardiovascular capacity. All obese patients, whose occupation is sedentary, should be advised to walk for at least an hour a day, always provided they are fit to do so. Regular daily exercise is much more valuable than episodes of activity at the week-end.

ANORECTIC DRUGS. Many drugs have been recommended as ‘slimming agents’. Critical assessment has disposed of the claims made on behalf of most of them except for a group known as the ‘anorectic drugs’ which include amphetamine, certain chemically related compounds and phenmetrazine.

Amphetamine and phenmetrazine stimulate the higher cortical centres and have been shown to have some limited value in the management of obesity. They create a sense of well-being which may help the patient to persevere with dietary restrictions. They may also stimulate the satiety centre in the hypothalamus and thus have a suppressive effect on appetite. Unfortunately these drugs are addictive and have been so widely abused that they are no longer recommended for the treatment of obesity. Other anorectic drugs without these disadvantages include fenfluramine and phentermine; they are quite expensive. In the case of fenfluramine, 20-40 mg given twice daily before meals, there is no danger of causing excessive excitability or producing dependence, since it is not metabolised in the body to amphetamine. In fact it has a mildly sedative action. Occasionally unpleasant side-effects are produced such as dry mouth, diarrhoea, dizziness and tiredness. Much more rarely confusion may become so marked that the drug has to be withdrawn.

Several incidents of fenfluramine poisoning have recently been reported, especially in children. Alarming reactions including convulsions, coma and even death have occurred when 20 or more tablets have been taken. It is therefore essential that the tablets should be stored in a place inaccessible to children.

Fenfluramine is a suitable anorectic drug for use in anxious patients who have become disheartened with the poor results achieved by diet alone. For patients of the lethargic type phentermine, 30 mg daily before breakfast, would be more suitable as it has a stimulating effect which may help the patient to persevere with the diet.

Anorectic drugs are no substitute for a dietary regime and the radical alteration of the patient's food habits. It is never justified to use these drugs at the beginning of treatment. If an obese person has failed to progress then an anorectic drug may be prescribed for periods not exceeding six weeks at a time; these drugs tend to lose their effect after regular use for a few weeks.

THYROXINE. The administration of thyroid hormone to euthyroid obese patients is not only useless but is potentially dangerous, especially if degenerative heart disease is present. Only if hypothyroidism co-exists with obesity should thyroxine be prescribed and then cautiously (p. 644).

METHYL CELLULOSE. This is an indigestible substance which adds bulk to the diet. It distends the stomach and so may help to allay hunger. In clinical trials it has been shown to have little if any effect in promoting weight loss, and it is very doubtful if this product is of any value as an adjunct to dietary therapy. However, it is quite harmless.

SURGICAL TREATMENT. In recent years operations such as small intestine bypass, aimed at inducing malabsorption, have been undertaken in some centres for the treatment of intractable cases of severe obesity. The side-effects have sometimes been distressing, and at present it seems unlikely that these experimental techniques will contribute substantially to the management of obesity.

CONTINUING SUPERVISION. The patient must be seen by a responsible supervisor, at first at intervals of no more than two weeks. With continuing success the interval may be extended to no more than four weeks. She should be advised against weighing more frequently than once weekly, because she may be alarmed or discouraged by irregularities in the rate of loss of weight, or sometimes slight increases due to retention of water. While loss of weight continues some words of approbation will be appreciated by the patient. If losses are not being recorded, an explanation must be forthcoming; if not, weighing the diet may be adopted for a period, or anorectic drugs may be given a trial for a period of no more than six weeks. The support of lay groups such as 'Weight Watchers', when available, should not be denied. The great majority of obese patients can be managed as out-patients, but in intractable cases admission to hospital may occasionally be necessary to prove to the patient that loss of weight invariably occurs with proper regulation of the food intake.

Prognosis. It is easy for an obese person to lose up to 5 kg in weight. This accounts for the temporary successes of numerous popular 'slimming cures'. How difficult it is to achieve further losses is not generally realised. The published records of seven obesity clinics in the USA showed that satisfactory results ranged only from 12 to 28 per cent if the index of success was the loss of 12 kg or more.

Experience in many clinics has shown also that it is difficult for patients to maintain their reduced weight. The reasons for these poor results are not clear, but must be related to failure of motivation in the patient, and to the inadequacies of the methods at present available for the control of obesity.

PREVENTION OF OBESITY

Prevention of obesity at present must depend in part on the doctor who discerns when his patients (be they infants, children or adults) are beginning to put on too much weight. Young mothers especially are apt to do so during and after a pregnancy. For this purpose alone, one of the most useful records that a doctor can keep about his patients is that of their weight, measured at regular intervals. Sudden, unexplained changes may not only warn of the threat of obesity but, in the opposite direction, can be the first indication of other diseases. The doctor's responsibility with an overweight patient, at any time is advisory and educational: he can and must draw the attention of his patients to the disadvantages and dangers of obesity and to the appropriate methods of correcting this, but he cannot cure the disability himself.

All the health agencies available should be mustered to support a steady campaign of education and persuasion of patients and potential patients on the need to avoid obesity. The antenatal services, infant welfare clinics, school health authorities, health visitors and many others to whom the public look for advice when they are in difficulties should serve as the medium for this educational programme.

In view of the dimensions of the problem at a national level, the points which follow should be emphasised at every opportunity.

1. Obesity is a serious disability with well-recognised penalties attaching when it is allowed to persist.
2. Responsibility for maintaining a normal weight is a personal matter which cannot be ignored or delegated.
3. Weighing at regular intervals, at least monthly, will provide reassurance or an early warning of deviation from a normal weight.
4. Habitual overeating will certainly be followed by a gain in weight, but this can also occur without any obviously excessive intake of food.
5. No age-group is exempt, and it is particularly important to prevent infants and young children from becoming overweight, as they may be initiating a life-long disability at this time.
6. Regular exercise is a normal physiological requirement and is part of the weight regulating mechanism.
7. Alcohol is a commonly abused source of extra energy. Account must always be taken of the calories added to the intake in this way.
8. Prevention of obesity is much easier than correcting the disability when it has become established.

J. A. STRONG.
A. S. TRUSWELL.

Further reading:

Cameron, M. & Hofvander, Y. (1971). *Manual on Feeding Infants and Young Children* (for application in the developing areas of the world with special reference to home-made weaning foods). New York: Protein Advisory Group of the United Nations System.

Davidson, Sir Stanley, Passmore, R. & Brock, J. F. (1972). *Human Nutrition and Dietetics*, 5th ed. Edinburgh and London: Churchill Livingstone.

Department of Health and Social Security (1969). *Recommended Intakes of Nutrients for the United Kingdom.* Reports on Public Health and Medical Subjects No. 120. London: H.M.S.O.

Food and Agricultural Organisation/World Health Organisation (1967). *Requirements of Vitamin A, Thiamine, Riboflavine and Niacin.* WHO Tech. Rep. Ser. No. 362, Geneva.

Jelliffe, D. B. (1966). *The Assessment of the Nutritional Status of the Community* (with special reference to field surveys in developing regions of the world). WHO Monograph Series No. 53. Geneva: World Health Organisation.

McCance, R. A. & Widdowson, E. M. (1960). *The Composition of Foods.* Medical Research Council Special Report Series No. 297. London: H.M.S.O.

Reichsman, F. (editor) (1972). *Hunger and Satiety in Health and Disease.* Basel: Karger.

Swedish Nutrition Foundation (1971). *Famine.* Uppsala: Almquist and Wiksells.

Wright, F. J. & Baird, Sir James (1974). *Tropical Diseases*, 5th ed. Supplement to *The Principles and Practice of Medicine*, 11th ed. Ed. Macleod, J. Edinburgh and London: Churchill Livingstone.

Note:

Reference values for various biochemical and haematological factors and their S.I. equivalents are given on pages 1008 to 1011.

Disturbances in Water and Electrolyte Balance and in Hydrogen Ion Concentration

THE chemical events collectively called metabolism require the concentration of hydrogen ions and electrolytes to remain within narrow limits in the tissue cells and in the fluid which bathes them. Derangement of water and electrolyte balance and disturbances in hydrogen ion concentration occur in a wide variety of clinical conditions which are separately described in the appropriate chapters of this book. It is convenient, however, to summarise here the relevant physiological facts and to describe briefly the more common abnormalities. The role of the kidney in regulating the water and electrolyte content of the body and in maintaining the normal acid-base equilibrium of the blood is described on pages 581 to 582.

NORMAL DISTRIBUTION OF WATER AND ELECTROLYTES

Water. The body of a normal man of 65 kg contains approximately 40 litres of water. About 28 litres of this is intracellular, and 12 litres extracellular. The latter is composed of 9-10 litres of interstitial fluid and 2-3 litres of plasma. Using tritiated water, it has been shown in human subjects that water readily passes through almost all membranes of the body and permeates easily into all fluid compartments. Its final distribution between the compartments is determined by osmotic and hydrostatic pressures and under normal conditions the total amount of water in the body is kept remarkably constant.

Electrolytes. The inorganic ions dissolved in the body water include sodium, potassium, calcium, magnesium, chloride, phosphate, bicarbonate and sulphate. These are not dispersed in the same concentrations throughout the various body fluid compartments. Sodium and chloride are confined mainly to the extracellular fluids where they are present in average concentrations of 142 mEq/*l* and 100 mEq/*l* respectively. These ions contribute the major part of the total osmolal concentration of the plasma and extracellular fluids. Potassium, magnesium, phosphate, and sulphate are present in highest concentration inside the cells where they maintain the osmolal concentration analogous to that of sodium and chloride in the extracellular fluids. In extracellular fluid potassium is present in a mean concentration of only 4·5 mEq/*l* and magnesium in a concentration of about 2 mEq/*l*. Bicarbonate is found in the fluid outside the cells and in the tissue cells themselves in concentrations of 25 mEq/*l* and 10 mEq/*l* respectively. Hydrogen ions are present in a concentration of only 40 nanoEq/*l*. They are present within cells at a higher concentration than in the extracellular fluids.

Because of the permeability of the capillaries, the concentration of electrolytes in the plasma and in the extracellular fluids in the tissue spaces is very similar. Interchange between these extracellular compartments is limited, however, in respect of protein molecules, the concentration of which is many times greater in the plasma than in the interstitial fluid. The volume of the plasma is largely the result of hydrostatic pressure which tends to force water outwards, and the osmotic pressure of the plasma proteins which draws water back into the vascular bed. In spite of the differences in the ionic pattern inside the cells as compared with that of the fluid which bathes them, under normal conditions the osmotic pressure is believed to be identical in extracellular and intracellular fluids. The differences in composition are established and maintained by the activity of ionic pumps within or near the cell membrane and are essential to life.

DISTURBANCES IN WATER AND ELECTROLYTE BALANCE

The complexity of the composition of body fluids is reflected in the variety of disturbances that may occur in them either as a result of disease or as a consequence of therapeutic endeavour and drug administration. Such disturbances not only contribute to the clinical picture of many diseases, but are themselves a hindrance to recovery. As a result, much of modern therapy is directed towards maintaining the chemical composition of the body fluids and correcting as far as possible any derangements that may arise. It is important that these disturbances are recognised and adequately treated. The labelling of such abnormalities simply as 'dehydration' and the indiscriminate use of intravenous isotonic, i.e. 'normal' saline in an attempt to correct them is to be deprecated. The more common disturbances in water and electrolyte balance are as follows:

1. Sodium depletion
2. Primary water depletion
3. Potassium depletion
4. Potassium excess and intoxication
5. Magnesium deficiency and intoxication
6. Water intoxication
7. Sodium and water accumulation.

Sodium Depletion

Normal sodium (salt) balance depends upon an equality between the amounts of sodium excreted and ingested. In health and in temperate climates negligible amounts of sodium are lost in the stools and from the skin. In the absence of renal disease the power of the kidneys to conserve sodium in the face of reduced intake is considerable and normal salt balance may be maintained with a very small daily intake. For these reasons sodium depletion generally occurs because of excessive loss of salt from the body rather than because of inadequate intake.

Because of the intimate relations of salt and water balance, loss of sodium is usually accompanied by a corresponding reduction in the water content of the body. *Pure* sodium depletion unattended by significant water loss is rare and probably occurs only as a result of abnormal loss of salt and water when an unrestricted intake of water has been permitted or encouraged. This may arise for example, from excessive sweating in unfavourable environments when fluid loss is replenished by salt-free liquids. In these circumstances the change in total body water may be negligible in spite of a considerable deficit of body salt. More commonly, however, conditions giving rise to sodium depletion are attended by some degree of water loss and unless large amounts of salt-free fluids have been given, the depletion is really a *mixed* one, though the salt loss usually predominates over the water loss.

Causes of Depletion. In temperate regions predominant sodium depletion arises as a result of excessive loss of salt in the urine or because of increased loss of sodium-containing fluids from the gastrointestinal tract.

Failure of the kidney to conserve salt may develop because of intrinsic renal disease or inadequate hormonal control. Examples are found in some patients with pyelonephritis (i.e. 'salt-losing nephritis'), the diuretic phase of acute renal failure of ischaemic origin, Addison's disease and to a lesser extent in hypopituitarism. Excessive loss of salt in the urine together with water loss occurs in the osmotic diuresis of uncontrolled diabetes mellitus. If diabetic ketoacidosis develops, urinary sodium loss is further increased as the mechanism for hydrogen ion secretion is unable to cope with the severe degrees of acidosis. Sodium depletion may also be induced by the excessive or prolonged use of diuretics.

Gastrointestinal causes of sodium depletion include all conditions involving external loss of salt-containing fluids, i.e. acute or chronic diarrhoea, intestinal fistulae, aspiration of gastrointestinal contents and vomiting.

Sweating is a well-known cause of sodium depletion in tropical countries and often aggravates the degree of sodium depletion caused by disease. Loss of sodium in the sweat is also important in children suffering from cystic disease of the pancreas.

Consequences of Predominant Sodium Depletion. As sodium is predominantly extracellular, salt depletion quickly reduces the volume of the extracellular fluids. Any disproportionate loss of salt to that of water tends to render the extracellular fluids hypotonic. This tendency however is mitigated by two events, (1) the volume of water excreted in the urine is initially increased in order to restore the normal total osmolal concentration, and (2) some extracellular water migrates into the cells so that the threatened extracellular dilution is minimised. As a result, there is a further diminution in the volume of extracellular fluid, including plasma, while the water content of the cells may even increase. The fact that predominant salt depletion chiefly affects the volume of the extracellular fluid is responsible for many of the clinical features such as loss of elasticity of the skin, diminution of intra-ocular pressure and dryness of the tongue. Thirst is not a prominent complaint, and its absence may be due to the hypotonicity of the body fluids. The decrease in blood volume leads to a fall in blood pressure and in the rate of glomerular filtration; oliguria then occurs. The capacity of the body to rid itself of urea diminishes and uraemia develops. The pulse rate rises. Selective vasoconstriction diminishes the circulation through the skin so that the skin and the limbs become pale and cold.

Although the plasma sodium concentration may be within normal limits, it may be reduced to 120 mEq/*l* or less in severe cases.

Treatment. The administration of water or of glucose in water in conditions associated with salt depletion is fraught with danger because the hypotonicity may be further aggravated. As more salt-free fluid is given, the kidneys respond by the excretion of large volumes of dilute urine in an attempt to restore the normal osmolal concentrations. The ill-effects of such treatment, moreover, are all too easily obscured by the conventional fluid balance chart which records only fluid intake and urine output, without reference to sodium balance. Adequate treatment consists of giving salt and water by mouth or an isotonic salt solution intravenously. The latter is required in all but very mild cases with normal blood pressure. Two to three litres of isotonic salt solution intravenously in two hours represents the usual adult requirements. In the more severe cases with marked circulatory impairment, deficits equivalent to 4-8 litres of isotonic salt solution occur. Such deficits should be repaired largely by isotonic sodium chloride. The first 2-3 litres should be given rapidly within the first two to three hours, the remainder being given within 24 to 48 hours. The best guides to the amount required are the disappearance of the signs of salt depletion and the restoration of normal blood pressure and pulse rate. Plasma sodium determinations are useful in controlling the treatment of severe cases, especially when the causative disease is likely to lead to continued salt loss, e.g. severe and persisting diarrhoea. Excessive administration of salt is to be avoided; the bases of the lungs should be frequently examined in order to detect crepitations, and the neck veins should be inspected to detect any increase in venous pressure.

Severe salt depletion is almost invariably associated with water depletion and disturbance in acid-base balance. Frequently potassium balance and occasionally magnesium metabolism are also disturbed. When accompanied by these disturbances the treatment of salt depletion requires to be modified accordingly.

Primary Water Depletion

Pure or predominant water depletion is one of the simplest of chemical disorders. The water content of the body is reduced both absolutely and relatively to the salt content, and the osmolal concentration of the extracellular fluids tends to rise. Between 600 and 1,000 ml of water is lost daily from the body in the expired air and by evaporation from the skin. This daily loss continues irrespective of the water intake. The urine is the other main channel of excretion of water but its volume can be reduced if necessary by increasing its concentration up to a limit determined by renal concentrating ability and the amount of solute to be excreted.

Causes of Water Depletion. Primary water depletion occurs less commonly in clinical practice than sodium depletion and usually arises because water intake is reduced below an amount necessary to maintain balance. This is liable to occur in patients who suffer from dysphagia or have obstructive lesions of the oesophagus or more simply in those who are comatose, depressed or apathetic, as is common, for example, in the aged. Water deficit then occurs because the intake falls below the amount being lost from the lungs and the skin. This obligatory daily loss of water from the lungs and skin is increased by hyperpnoea or pyrexia. Excessive loss of water in the urine is a less common cause of water depletion but occurs in patients in whom the renal power of concentration is restricted, as for example in diabetes insipidus, hyperparathyroidism and in water-losing nephritis.

Consequences of Water Depletion. As water is lost from the body the extracellular fluid becomes hypertonic. Water then migrates from the cells in accordance with this increase in osmotic pressure and intracellular dehydration occurs. The overall body water loss is thus shared by the extracellular and intracellular fluids. For this reason the circulatory signs of dehydration are not so obvious as those of salt depletion. Thirst is usual unless the patient is senile or confused. The migration of water from the cells to the extracellular fluids helps to maintain the volume of the extracellular fluid nearly within normal limits for a time, so that the blood pressure, packed cell volume, and plasma and blood concentrations remain unaltered until considerable depletion has occurred. The patient, however, may exhibit mental confusion or complain of vertigo and difficulty in swallowing. In severe cases the skin and tissues acquire a curious 'doughy' consistency. Ultimately renal blood flow is reduced and the blood urea concentration rises. The plasma sodium concentration and the packed cell volume then become elevated.

Treatment. Water depletion should be treated by giving salt-free fluids. The use of isotonic sodium chloride solution is contraindicated. If the patient is conscious and is not vomiting, water should be given by mouth until thirst is quenched and thereafter amounts of between 1·2 to 2·5 litres per day are usually sufficient. If the patient is unable to swallow fluids in sufficient amounts, 5 per cent glucose in water should be given by intravenous infusion. The amount required varies with the degree of depletion. In moderately severe cases 2-4 litres of 5 per cent glucose in the course of 24 hours is usually sufficient. In severe water depletion, 5-10 litres may be needed. The best guides to the amount of fluid required are the clinical improvement of the patient and the increase in the volume of urine, which should rise to about 1·5 litres per 24 hours. If water depletion is due to water-losing renal diseases, it may be necessary to continue to give large daily amounts of water.

It must be remembered that when water depletion is associated with salt loss, isotonic salt solution and water are both required and should be given together in amounts determined by clinical assessment of the relative degrees of the two deficiencies.

Potassium Depletion

Potassium depletion is responsible for various clinical features in a wide variety of diseases. Depending upon the daily intake, the healthy individual in potassium balance excretes about one-third of his daily potassium intake in the stools and two-thirds in the urine. The bulk of urinary potassium is excreted by the cells lining the distal renal tubules in response to the electrical potential gradient created largely by active sodium reabsorption. Diffusion of potassium at this site is also affected by the acid-base state (Fig. 77, p. 580).

Causes of Potassium Depletion. Potassium depletion occurs as a result of excessive loss of potassium from the gastrointestinal tract or in the urine.

Alimentary loss occurs as a result of acute severe or chronic diarrhoea, vomiting, fistulous drainage or aspiration.

Renal wastage of potassium is more complex in its development. It occurs: (1) in circumstances which lower the efficiency of the cellular ionic pump throughout body cells; since almost all of the potassium in the body lies within the cells, potassium depletion and increased urinary loss ensue; such factors include hypoxia, impaired oxidation of carbohydrate and acidosis of metabolic or respiratory origin; (2) in circumstances which favour the passive diffusion of potassium into the lumen of the distal tubule. These include:

(*a*) disorders such as Cushing's syndrome and aldosteronism, the administration of large amounts of sodium-containing fluids, the diuretic phase of acute renal failure, and the use of diuretics, carbenoxolone or corticosteroids;

(*b*) drugs or diseases which reduce tubular secretion of hydrogen ions; these include carbonic anhydrase inhibitors such as chlorothiazide and diseases such as renal tubular acidosis and respiratory and metabolic alkalosis;

(*c*) elderly people who take a diet inadequate in potassium; the cause is uncertain but it is most likely due to continued urinary loss.

Consequences and Clinical Features of Potassium Depletion. Significant depletion of potassium may occur without alteration in the plasma potassium concentration and the diagnosis of intracellular potassium deficit is made difficult by the inaccessibility of the intracellular fluid to analysis. Biochemical evidence of potassium lack may be suggested by an elevation in plasma bicarbonate concentration or a diminution in plasma sodium concentration. These effects are believed to be due to the migration of hydrogen and sodium ions from the extracellular into the intracellular fluids. Symptoms attributable to potassium deficiency include apathy, muscular weakness, mental confusion and abdominal distension. It is clear that such features arise in the course of many diseases. Nevertheless, their occurrence in circumstances which are known to lead to potassium deficiency, and their relief after potassium administration justify the diagnosis. Potassium depletion reduces the ability of the kidney to concentrate; hence polyuria and thirst commonly occur. Potassium depletion also gives rise to increased susceptibility to intoxication with digitalis. Severe potassium depletion lowers the cardiac output and this may give rise to oedema.

Potassium deficiency sufficiently severe to be associated with reduction of the plasma concentration is more easily recognised, but is less common than simple intracellular depletion. It may occur in any of the conditions mentioned above if the deficiency is severe enough and is particularly liable to develop in cases of diabetic ketoacidosis which have been vigorously treated with sodium containing solutions or glucose and insulin; this therapy causes a migration of potassium from the extracellular to the intracellular space with resulting hypokalaemia. The clinical picture of extracellular potassium deficit is characterised by generalised muscular weakness with paresis or flaccid paralysis and ileus. Paraesthaesiae are also commonly present. The electrocardiogram commonly shows a small T wave and ST depression. Death may occur if treatment is inadequate.

Treatment. Potassium depletion should be treated by giving a potassium salt orally or intravenously. The former route is more commonly used and is less dangerous than parenteral administration. The normal daily intake of potassium is about 2-3 g.

(1) Established deficiencies of moderate severity (about 400 mEq) can be remedied by giving 10-15 g of potassium chloride per day orally, in divided doses for some days in addition to a diet rich in potassium, i.e. containing fruit and fruit juices.

Potassium chloride tablets, even when enteric coated, are sometimes irritating to the gastrointestinal tract. 'Slow release' tablets of potassium chloride are less troublesome in this respect, each tablet containing 600 mg of KCl. Some patients tolerate effervescent potassium tablets more readily and these appear to be less nauseating. Each tablet contains 250 mg of potassium. Some effervescent tablets contain chloride which is useful in correcting the metabolic alkalosis which is associated with potassium depletion and which is frequently due to concurrent chloride depletion (p. 202).

(2) Intravenous infusions of potassium chloride are needed for patients who are unable to take potassium by mouth, but should be given only when the existence of hypokalaemia is established by chemical analysis. Such infusions should rarely be given in the presence of anuria or oliguria and only when facilities for repeated chemical analysis are available.

If oliguria is due to associated water and salt depletion these should be treated first. For intravenous administration, potassium chloride (1·5 g in sterile ampoules) can be conveniently added to 500 ml of isotonic salt or 5 per cent glucose solution. The solution then contains 40 mEq/*l* and should be given slowly over two to three hours. Repeated determinations of the plasma potassium are necessary to determine whether further infusions are required. Administration of potassium by mouth should be started as soon as possible, as the major portion of the deficit can be corrected only by this means. When the depletion of potassium has arisen because of persistent vomiting and is associated with alkalosis due to loss of gastric hydrochloric acid, potassium is conveniently given with sodium and ammonium chloride as described on page 204. Prophylactic administration of potassium chloride (3-4 g daily) or effervescent potassium tablets should be given to patients who are being treated by drugs known to increase urinary loss of potassium. These include corticosteroids and many diuretics (p. 196).

Potassium Excess and Intoxication

Causes. Abnormal accumulation of potassium in the blood and extracellular fluid usually occurs in association with severe oliguria or anuria. It is commonly found in conditions leading to acute renal failure, e.g. circulatory failure from blood loss or injury and severe cases of Addison's disease and Addisonian crisis; it may occur in diabetic ketoacidosis prior to adequate treatment with insulin and intravenous solutions. Some patients in the terminal stages of chronic renal failure develop hyperkalaemia especially if potassium supplements are being given.

Consequences of Potassium Excess. Patients with hyperkalaemia are dull and lethargic and gradually become confused. Asthenia develops and progresses to flaccid paralysis. These features are indistinguishable from those of hypokalaemia. The pulse becomes irregular and bradycardia develops from heart block of variable degree. Hyperkalaemia is of considerable clinical importance because of the danger of cardiac arrest with levels of plasma potassium above 7·5 mEq/*l*. The diagnosis is made more frequently by knowing the circumstances in which intoxication is likely to arise and confirming the suspicion by plasma potassium analysis than from any specific clinical feature. Typical electrocardiographic changes occur; these include increase in the amplitude of the T wave, atrioventricular and intraventricular conduction defects and ultimately ventricular arrest.

Treatment. It is important to prevent the occurrence of potassium intoxication in conditions associated with oliguria and anuria. The recommendations made with regard to the diet in acute renal failure (p. 610) are designed with this aim in view. When dealing with an established case of hyperkalaemia, the following measures are advised:

(*a*) Immediate restriction of foods rich in potassium (e.g. fruit juices) and in protein.

(*b*) The repair of any associated depletion of water or salt with the aim of re-establishing a normal circulation as early as possible and the correction of metabolic or respiratory acidosis by appropriate methods (pp. 202 and 332).

(*c*) The sodium or calcium loaded ionic exchange resin (Resonium A and Zeocarb) absorbs potassium in the intestine from the blood and intestinal secretions and contents. A suspension of 30 g in a small volume of water should be given by mouth three or four times per day or as required. In the event of vomiting the resin may be administered as a retention enema.

(*d*) The administration of glucose and insulin in order to encourage migration of potassium from the extracellular fluids into the cells. Ten units of soluble insulin subcutaneously and 50 g glucose by mouth should be given and may be repeated every two to four hours. The beneficial effect of this treatment is increased if $\frac{1}{2}$ to 1 litre isotonic sodium bicarbonate is given simultaneously by intravenous injection.

(*e*) Calcium gluconate (10 per cent), 10 ml given intravenously and repeated in two to three hours, has been shown to reduce the cardiotoxic effect of potassium.

(*f*) If these methods fail or if the rise of concentration of potassium is rapid, removal of potassium by peritoneal or haemodialysis is indicated.

Magnesium Deficiency and Intoxication

Rapid methods for determination of magnesium in body fluids now available have shown that disorders of magnesium metabolism are occasionally responsible for otherwise puzzling clinical features and are susceptible to therapeutic control.

Magnesium Deficiency. The most frequent cause of magnesium deficiency is prolonged diarrhoea or vomiting, which has been treated with parenteral fluid without magnesium supplements. It occasionally follows long continued diuretic therapy, and it is associated with chronic diarrhoea and severe undernutrition, such as occurs in kwashiorkor and the malabsorption syndrome. Aldosteronism, hyperparathyroidism and chronic alcoholism also lead to magnesium deficiency.

Clinical features are predominantly neuromuscular with tremor, choreiform movements and aimless plucking of the bedclothes. Mental depression, confusion, agitation, epileptiform convulsions and hallucinations also occur. The diagnosis should be confirmed by finding the concentration of magnesium in the plasma to be less than 1·5 mEq/*l*.

Magnesium deficiency is best treated parenterally; 100 mEq of magnesium sulphate (12 g $MgSO_4$ $7H_2O$) may be added to 1 litre of 5 per cent glucose or other isotonic solution and given over a period of 12 to 24 hours. The infusion should be repeated daily until the serum concentration remains within the normal range.

Magnesium Intoxication. This mainly occurs in acute and chronic renal disease and contributes to the central nervous features associated with uraemia (p. 607). Its treatment is that of the primary disorder.

Water Intoxication

Healthy individuals can safely drink very large volumes of water and respond to this by a vigorous water diuresis. The capacity of the body to excrete water when given without electrolytes is dependent upon many factors which include the rate of glomerular filtration and the power of the distal tubules of the kidney to produce a dilute urine. Many patients who are ill for a variety of reasons have a restricted ability to dilute the urine when given large amounts of water. These include patients suffering from acute and chronic renal disease, severe heart failure, adrenocortical insufficiency and hepatic cirrhosis. Occasionally tumours of the lung or ovaries secrete a polypeptide with antidiuretic properties which leads to water intoxication. Post-operative subjects are also incapable of diluting the urine because of the liberation of vasopressin by the stress of the operation. In all these circumstances even a modest water intake reduces the plasma osmolality and the concentration of sodium and produces symptoms which are primarily those of disordered cerebral function; these include dizziness, headache, nausea and mental confusion. Severe water intoxication can produce convulsions, coma and death. Diagnosis depends upon being aware of the circumstances in which water intoxication is likely to occur and the demonstration of a plasma sodium concentration below 130 mEq/*l*.

Treatment consists of restricting water intake for a few days. In severe cases 100 ml 5 per cent sodium chloride solution should be given intravenously and repeated in a few hours if there is little or no response. The use of fludrocortisone is beneficial in cases of hyponatraemia due to tumours and is also indicated in Addison's disease.

Sodium and Water Accumulation

In health, the total amount of sodium in the body is kept within narrow limits in spite of great day-to-day variations in the amount ingested. Positive sodium balance with consequent accumulation of sodium in the body results from a renal excretion that is inadequate in relation to the amount ingested. The accumulation is generally accompanied by the retention of water so that the concentration of sodium in the extracellular space is usually not materially altered. When the distribution of the retained fluid is generalised, the expansion in the volume of the extracellular space does not become clinically detectable until the increase is of the order of 15 per cent.

The primary mechanisms responsible for the accumulation of water and salt which lead to oedema vary with the nature of the disease and they are discussed in the appropriate sections of this book. They include reduction in the osmotic pressure from hypoproteinaemia as occurs in the nephrotic syndrome; an increase in venous hydrostatic pressure with migration of fluid from the vascular space to the tissue spaces is an important factor in heart failure and primary renal retention of salt and water is responsible in acute proliferative glomerulonephritis. In addition several compensatory reactions occur which promote further retention of water and salt. These include a rise in the levels of circulating vasopressin and also an increased secretion of aldosterone mediated by the renin angiotensin system (p. 582). The therapeutic use of cortisone, corticotrophin or testosterone may also give rise to water and sodium retention by virtue of their action on the kidney. Some oedema is not uncommon in normal women during the premenstrual stage of the menstrual cycle, but the mechanism of this is unknown. Oedema may be present in pregnancy and this may be due either to renal disease or to pre-eclampsia. Other disorders associated with generalised oedema include nutritional oedema and thiamine deficiency. In some diseases several mechanisms appear to be operating simultaneously. This is exemplified particularly in the oedema and ascites of hepatic cirrhosis in which portal hypertension, hypoproteinaemia and possibly salt retaining and antidiuretic hormones all contribute. It has to be admitted, however, that the knowledge of the cause of oedema in the above-mentioned diseases is far from complete. The clinical features of water and salt excess depend to some extent upon the distribution of the retained fluid. These are described under the various diseases in their respective sections.

Principles of Treatment. The principles guiding therapy are as follows:

(*a*) The use of measures designed to remedy specific factors leading to the oedema. These include digitalis in heart failure, corticosteroids in some forms of glomerulonephritis, the intravenous administration of plasma proteins or salt-poor albumin in conditions associated with hypoproteinaemia, and a high protein diet in oedema of nutritional origin, hepatic cirrhosis and the nephrotic syndrome.

(*b*) The depletion of the body of salt and water by the use of effective diuretics.

(*c*) The restriction by dietary means of the raw materials necessary for the formation of extracellular fluid, i.e. water and salt. The necessity for these restrictions has been greatly modified with the introduction of modern diuretics.

Diuretic Therapy. Before the discovery of modern diuretics oedema was a persisting and serious complication of several diseases, but nowadays it is rare for oedema to be resistant to treatment and the vast majority of patients who suffer from it can be totally relieved. The greatest advance has been the discovery of drugs which block renal tubular reabsorption of sodium. As a result of this effect, these agents induce negative sodium balance and by increasing the amount of solute particles in the tubular fluid a large volume of water is eliminated. The treatment of oedema by these diuretics is generally successful even when the pathological processes leading to water and salt retention are beyond therapeutic control. The following are the most important diuretics.

Thiadiazine diuretics exert two separate effects on renal function. They depress distal tubular reabsorption of sodium but they also inhibit carbonic anhydrase and sodium bicarbonate reabsorption in the proximal convoluted tubules. This double effect promotes sodium chloride and sodium bicarbonate loss. Potassium depletion occurs because of the delivery of increased amounts of sodium to the distal tubule. In addition potassium depletion is further aggravated by the reduction of the availability of hydrogen ions consequent upon carbonic anhydrase inhibition. Thiadiazine diuretics in common use are hydrochlorothiazide (100 mg) and bendrofluazide (10 mg).

The thiadiazine diuretics are particularly useful in the treatment of heart failure and in the nephrotic syndrome. Because of their tendency to produce potassium depletion and the neurological features of hepatic insufficiency they are sometimes less valuable than other diuretics for the treatment of oedema of hepatic cirrhosis (p. 564). Toxic reactions are rare but hyperglycaemia and diabetes are occasionally produced in susceptible patients in whom there is a family history of the disease. A rise in uric acid also occurs and for this reason the drugs are best avoided in gout or when the blood concentration of uric acid is elevated. The occurrence of agranulocytosis and thrombocytopenia has occasionally been observed.

Chlorthalidone (100-200 mg by mouth) is a sulphonamide derivative similar in its action to the thiadiazine drugs. It produces a slower and more prolonged diuresis extending over 48 hours.

Frusemide is chemically unrelated to the diuretics discussed above. This substance may be given orally (40-80 mg) or intravenously (10-20 mg). The onset of the diuresis is extremely rapid and is generally complete within six hours. Frusemide also causes potassium loss. It appears to eliminate a greater volume of water than can be accounted for solely by the osmotic effect of sodium within the renal tubules.

Ethacrynic acid is another diuretic of considerable potency and represents a new class of diuretics. It is given orally in doses of 50-200 mg per day. As in the case of frusemide it appears to eliminate a greater volume of water than can be accounted for by the osmotic effect of sodium. Indications for its use are similar to those for frusemide.

Amiloride (20 mg) and *triamterene* (200 mg) are much less potent diuretics than any of the thiadiazines but do not lead to potassium deficiency. This may be due to the fact that their natruretic effect is due to inhibition of sodium reabsorption in the distal tubule so that potassium secretion is not encouraged. Amiloride and triamterene are not diuretics of first choice and are generally used in conjunction with other diuretics.

ADVERSE EFFECTS OF DIURETIC THERAPY. Abnormalities in electrolyte balance which may occur following intensive diuretic therapy include potassium depletion and, more rarely, sodium depletion.

Potassium Depletion. Thiadiazine diuretics, frusemide and ethacrynic acid produce potassium depletion, especially when given repeatedly over long periods of time and when combined with diets low in sodium. Symptoms of potassium deficit may arise before satisfactory loss of oedema has been achieved and are then superimposed upon the clinical features of water and sodium accumulation. This state of affairs is especially prone to develop in the treatment of the more severe grades of cardiac failure. The complication is particularly unfortunate since it may be responsible for increased sensitivity to digitalis, with the development of toxic manifestations to this drug before adequate digitalisation and control of the heart failure has been attained. In hepatic disease with oedema and ascites the potassium depletion may seriously aggravate or precipitate the neurological features of hepatic insufficiency. Once severe potassium deficiency has occurred in these conditions, restoration of the normal body content may be extremely difficult and even impossible. It is for this reason that prophylactic administration of potassium is essential when diuretics are being given for long periods.

Sodium Depletion. Excessive administration of diuretics is capable of giving rise to severe sodium depletion and is more likely to occur with the use of frusemide and ethacrynic acid than with other diuretics. This low salt syndrome is especially likely to occur when treatment is long continued and when additional mechanical methods such as abdominal paracenteses are being used. These patients exhibit some of the features of sodium depletion although they are still oedematous. They become apathetic and suffer from anorexia and vomiting. The circulatory characteristic of sodium depletion is present, namely hypotension with an increase in the pulse rate. Chemical analysis shows that the blood urea concentration is increased and that the plasma sodium concentration is reduced to 130 mEq/*l* or less. Such patients are usually seriously ill and, when the oedema is cardiac in origin, may be in the last stage of their disease. Persistent attempts to reduce the oedema by any of the measures described above lead to further clinical deterioration. These remedies should be withheld and a diet unrestricted in its salt content permitted. In a few instances the intravenous administration of hypertonic saline may be dramatically successful in relieving the symptoms of the low salt syndrome. Two hundred ml of 5 per cent saline should be given slowly by intravenous infusion, and may be repeated after 24 hours.

TABLE 3

Causes of water and electrolyte imbalance

Predominant Sodium Depletion	Potassium Depletion	Primary Water Depletion
Acute severe diarrhoea Chronic diarrhoea Vomiting Aspiration of gastro-intestinal contents Intestinal fistulae Diabetes mellitus and diabetic ketoacidosis Chronic nephritis and pyelonephritis (salt-losing) Diuretic phase of acute renal failure Addison's disease Hypopituitarism Excessive sweating (with unrestricted water intake) Excessive use of diuretics	Acute severe diarrhoea Chronic diarrhoea Vomiting Aspiration of gastro-intestinal contents Malabsorption syndrome Chronic starvation and anorexia Diabetes mellitus and ketoacidosis (after treatment) During and after treatment with corticosteroids and corticotrophin Excessive use of diuretics and of carbenoxolone Cushing's syndrome and aldosteronism Post-operative period Acidosis and alkalosis Dehydration Chronic tissue hypoxia (e.g. heart failure)	Apathy due to illness, senility, psychosis Diseases causing dysphagia Coma Diabetes insipidus and other renal water-losing conditions, e.g. hyperparathyroidism
Sodium and Water Excess (generalised oedema)	Potassium Excess and Intoxication	Water Intoxication
Cardiac failure Hepatic cirrhosis Nephrotic syndrome Acute glomerulonephritis Excessive use of corticotrophin, corticosteroids and testosterone Premenstrual phase of cycle Pre-eclampsia Malnutrition	Diabetic ketoacidosis (before treatment) Peripheral circulatory failure from burns and blood loss Acute renal failure (oliguric phase) Addison's disease Chronic renal disease	Post-operative period Renal disease Adrenocortical insufficiency Severe heart failure and hepatic cirrhosis ADH secreting lung carcinomata
		Magnesium Depletion
		Malabsorption syndrome Diarrhoea Vomiting Aldosteronism Hyperparathyroidism Long continued diuretic therapy Diuretic phase of acute ischaemic renal failure Chronic alcoholism
		Magnesium Intoxication
		Renal failure

Diagnosis of Disturbances in Water and Electrolyte Balance

It is apparent from this summary of the consequences of body depletion of sodium, water, potassium and magnesium and of potassium and magnesium intoxication that these disturbances present considerable diagnostic difficulty and are not characterised by pathognomonic signs or symptoms. The apathy of potassium depletion is indistinguishable from that of hyperkalaemia; severe sodium depletion is attended in the majority of instances by considerable water deficit so that these cases do not exhibit a clearly defined clinical picture. Furthermore, it is not uncommon for dual electrolytic deficits to develop simultaneously. For example, in diabetic ketoacidosis, potassium depletion may occur in conjunction with predominant salt depletion. In addition the symptoms of lethargy, apathy and mental confusion are common accompaniments of many diseases in which no significant body fluid distortion exists.

It has also to be recognised that the results obtained from biochemical analyses of blood by routine procedures are of only limited diagnostic value. Potassium or magnesium deficit may occur without significant alteration in their plasma concentrations, and serious sodium depletion may develop with plasma sodium concentrations within the recognised limits of normality. A low plasma sodium may not even indicate salt depletion, and hyponatraemia is frequently seen in the late stages of malignant disease, generalised tuberculosis and more rarely in association with vasopressin secreting tumours or other causes of water intoxication.

Accurate diagnosis largely depends upon a knowledge of the conditions and diseases which may give rise to abnormalities in water and electrolyte balance. In the presence of such diseases, the suspicion that these abnormalities may exist is strengthened by the presence of the clinical features known to occur with them and possibly by the results of appropriate biochemical and electrocardiographic examinations (Table 3).

By understanding the mechanism by which the economy of the fluids of the body becomes disturbed and by the intelligent use of the reparative fluids which have been described, much can be done to restore the distortions of body fluid balance wrought by disease.

HYDROGEN ION CONCENTRATION

Life is possible only if the blood is kept within a range of alkalinity, and in health a physiological hydrogen ion concentration corresponding to a pH of between 7·35 and 7·45 is maintained by two widely different mechanisms which are closely integrated. A proper understanding of these mechanisms is necessary for a full appreciation of the clinical implications of acidosis and alkalosis.

The blood is alkaline because it contains bicarbonate, phosphate and proteins which are quite strong bases. It also contains carbonic acid and the pH of the blood depends principally upon the ratio of the main acid component, carbonic acid and the main base bicarbonate. The concentration of carbonic acid in the plasma is determined by the partial pressure of carbon dioxide (P_{CO_2}) in the alveoli. The latter is normally about 40 mm Hg and this gives rise to little over 1 mEq/*l* of carbonic acid in physical solution in the plasma. The alveolar partial pressure of carbon dioxide is itself maintained steady by the equality between its rate of production by the tissues and the rate at which ventilation eliminates it from the body. On the other hand, the concentration of bicarbonate is regulated by the tubular epithelium of the kidneys and in health is kept at about 22-24 mEq/*l* by the mechanism described on page 581. A great many metabolic processes result in the production of acids and these must be eliminated from the body if the reaction of the tissue and the blood is to remain within the normal range. The route of disposal of these acids depends upon whether or not they are capable of being oxidised completely to carbon dioxide and water. Carbon dioxide forms carbonic acid within the body and is eliminated as carbon dioxide by ventilation. Other acids such as acetoacetic acid or sulphuric acid which are derived from the oxidation of fatty acids or sulphur-containing proteins respectively are excreted by the kidneys. At the site of their production in the tissues and during their carriage in the blood all acids increase the hydrogen ion concentration. The extent of this increase is minimised by the stabilising power of the blood and tissues which in turn depends on the presence of the physiologically important buffers.

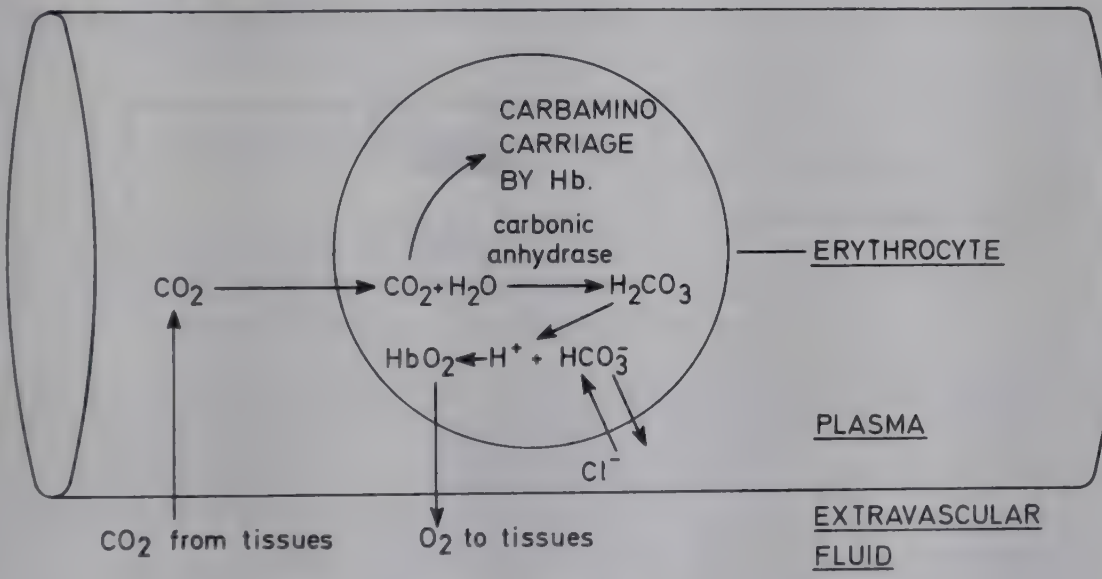


FIG. 19

TRANSPORT OF CO_2

Carbonic acid is produced by metabolic reactions in far greater amounts than any other acid. A small part of the carbon dioxide is transported in the blood reversibly bound to haemoglobin as a carbamino compound. A greater part is converted to carbonic acid in the red blood cells under the influence of carbonic anhydrase, and is then buffered by haemoglobin when it gives its oxygen to the tissues and is converted to reduced haemoglobin (Fig. 19). The hydrogen ions of the carbonic acid are taken up by the haemoglobin in the red cells while the bicarbonate ion moves out from the red cells to the plasma in exchange for chloride ions (chloride shift). Most of the carbonic acid added to the blood therefore appears not as acid but as bicarbonate ion. When the blood passes through the lungs and the haemoglobin is re-oxygenated this process is reversed and the carbon dioxide formed is expelled by ventilation.

In health a small amount of inorganic acid is produced each day and being non-volatile requires to be excreted by the kidney. Only a small amount of organic acid is produced in normal conditions but in diabetic ketoacidosis for example a large amount of acetoacetic acid is formed. The tissue and blood are buffered against these acids by a different mechanism which involves in particular the sodium bicarbonate and carbonic acid buffer system in the plasma. The addition of acid to the plasma results in a movement of the reactions in the direction indicated by the broad arrow (Fig. 20). As a result of this and of a similar reaction on the part of the other buffer systems, many of the hydrogen ions which would otherwise increase the acidity of the plasma are removed to form increased amounts of carbonic acid. There is a corresponding diminution in the concentration of bicarbonate ions. By this means the pH of the plasma falls far less than it would do if the buffers were not present. The fall in pH stimulates ventilation and the excess carbonic acid is removed from the body as carbon dioxide. The anion of the acid (e.g. acetoacetate) and the depleted body bicarbonate are dealt with simultaneously by the kidney. The renal tubules form carbonic acid, much of the hydrogen ion of which is used to form ammonium ions which are then excreted in the urine with the acid anion. The bicarbonate ion generated in this process is returned to the blood and reconstitutes the depleted blood buffer.

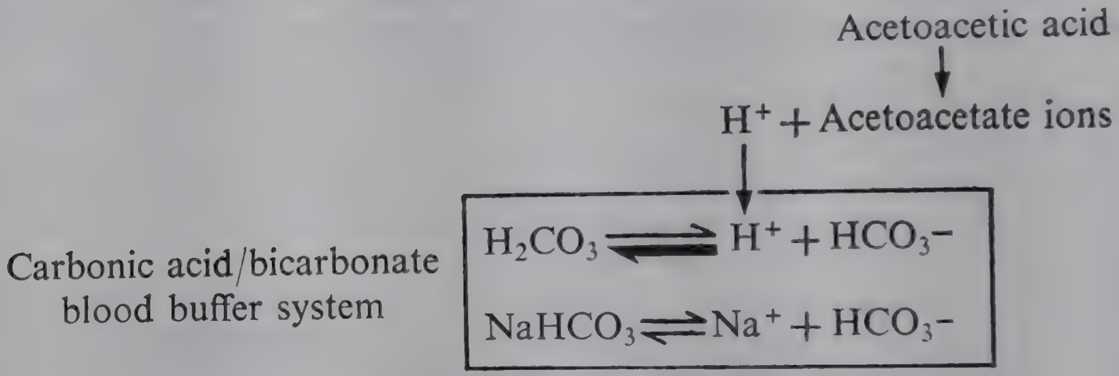

Acetoacetic acid
H^+ + Acetoacetate ions
Carbonic acid/bicarbonate blood buffer system
$H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$
$NaHCO_3 \rightleftharpoons Na^+ + HCO_3^-$

FIG. 20 Carbonic acid/bicarbonate Blood Buffer System

These buffering and excreting mechanisms are continually in operation in response to the normal production of acids derived from the food and its metabolism. It is clear from this simplified description that the important limiting factor in the buffering power of blood is the available haemoglobin and bicarbonate. The excreting power of the kidneys is the limiting factor in the body's ability to rid itself of anion derived from inorganic and organic acids other than carbonic acid.

DISTURBANCES IN HYDROGEN ION CONCENTRATION

Abnormalities in the reaction of the body fluids are reflected in changes in the concentration of carbonic acid (i.e. $PaCO_2$) and by alterations in body base, notably that of bicarbonate. The estimation of $PaCO_2$ is of particular value in respiratory disorders and its use in these conditions is described on page 329. Unfortunately there is no entirely satisfactory method available for the determination of [HCO′$_3$]. Nowadays it is usually calculated from a knowledge of Pa_{CO_2} and pH using the Henderson Hassalbach equation. Since the concentration of bicarbonate is itself influenced by Pa_{CO_2} it is common practice to express the [HCO′$_3$] as the concentration which would exist at a standard value of Pa_{CO_2} of 40 mm Hg. It is then known as standard bicarbonate and normally ranges between 22 and 26 mEq/*l*.

Metabolic Acidosis

Metabolic acidosis arises as a result of the production or ingestion of acids other than carbonic acid, or as a consequence of body depletion of the base bicarbonate. The condition is characterised by a fall in pH and a marked reduction in the concentration of bicarbonate in the plasma. The Pa_{CO_2} is reduced secondarily by the hyperventilation produced by stimulation of respiration; this mitigates to some extent the reduction in pH which arises from the fall in [HCO′$_3$].

The production of large amounts of lactic acid in vigorous exercise is probably the most common cause of acidosis and is to be regarded as physiological. Shock causes metabolic acidosis because of hypoxia of the tissues and the accumulation of organic acids, particularly lactic acid. Other important causes of acidosis are diabetic ketoacidosis and renal failure. In the former condition, β-hydroxybutyric acid and acetoacetic acid are produced in abnormally large amounts, and at a rate which is greater than the capacity of the body for their oxidation. In patients with acute or chronic renal failure, the power of the kidneys to conserve and generate bicarbonate ions and to produce and secrete hydrogen and ammonium ions is impaired and their excretion is diminished.

Depletion of body bicarbonate occurs from direct loss of sodium bicarbonate in the stools in chronic or severe acute diarrhoea or from loss of intestinal contents from fistulae or by intestinal aspiration. The therapeutic administration of acetazolamide (Diamox) for glaucoma may also give rise to acidosis. Acetazolamide depresses the power of the kidneys to generate bicarbonate and secrete hydrogen ions which then accumulate in the blood. Ammonium chloride is used in the treatment of severe metabolic alkalosis (p. 204); the ammonium radical is converted to urea, and the hydrochloric acid remaining reduces the alkalosis.

Consequences of Metabolic Acidosis. The most obvious consequence of acidosis is the stimulation of the respiratory centre by the abnormally high blood concentration of hydrogen ions. In severe cases the respirations become deep and rapid (Kussmaul's respiration). It is clear, however, from the list of causes given above that the clinical picture in the individual case is largely determined by the underlying condition and by the presence of other concomitant disturbances in water and salt balance. By the time acidosis is severe in diabetic ketoacidosis, considerable water and salt depletion has usually occurred. The acidosis of chronic diarrhoea is similarly associated with salt loss and especially with potassium deficit. The failure of ammonium and hydrogen ion production by the kidney in chronic nephritis, which leads to acidosis, is necessarily accompanied by abnormal loss of sodium and potassium in the urine. As in the case of disturbances in water and electrolyte balance, the diagnosis of metabolic acidosis is facilitated by an awareness of those pathological conditions in which it is likely to arise. The diagnosis should be confirmed by the determination of the concentration of bicarbonate in the blood. In acidosis of moderate degree this value is reduced to 15 mEq/*l*, while concentrations below 10 mEq/*l* represent severe degrees of acidosis.

Treatment. Since metabolic acidosis is commonly associated with some degree of salt depletion and water deficiency, it is reasonable to correct these disturbances, in the first instance, by the administration of isotonic sodium solution (p. 188); this is a neutral solution and by itself might be expected to have only a little influence on the reaction of the blood and tissues. In fact, provided the kidneys are not primarily diseased and provided the degree of salt and water depletion is not so severe as to impair renal function seriously, its intravenous administration is usually effective in correcting metabolic acidosis of moderate severity. Its success depends upon the capacity of the kidneys to generate bicarbonate from carbon dioxide and water and to retain this with the infused sodium, rejecting the chloride in the urine (p. 581).

In the presence of renal disease, severe acidosis and severe salt depletion giving rise to uraemia, it is unwise to depend upon the collaboration of the kidney for the alkalising effect of sodium chloride. In these circumstances, isotonic sodium bicarbonate should be given by intravenous infusion in addition to isotonic sodium chloride. The two solutions should be given in a ratio of 1 to 2 and need not be mixed. The total volume of the combined solutions required varies with the severity of the salt depletion and with the degree of acidosis. A moderately severe case of diabetic acidosis, for example, may require as much as 4-6 litres in the first 24 hours, of which 1-2 litres should be the isotonic sodium bicarbonate solution. The latter infusion should be given for as long as there is evidence of acidosis, as determined by the estimation of the bicarbonate concentration in the blood. When this has returned to normal levels, it may be necessary to continue the intravenous infusion of isotonic sodium chloride alone. This is indicated if there is still evidence of predominant salt depletion.

In severe shock or cardiac arrest due, for example, to myocardial infarction, acidosis develops without salt depletion. In these circumstances it is best to give sodium bicarbonate in a small volume of hypertonic concentration, i.e. 200-300 ml 5 per cent solution intravenously in the course of 10 to 15 minutes.

Metabolic Alkalosis

Metabolic alkalosis arises most commonly as a result of the abnormal loss from the body of hydrochloric acid in the course of prolonged or severe vomiting. Chloride deficiency itself also leads to alkalosis by stimulating the renal tubular reabsorption of bicarbonate. More rarely alkalosis may arise from the ingestion of large amounts of sodium bicarbonate given, for example, in the treatment of peptic ulcer. This is especially likely to occur if there is associated pyloric spasm or stenosis, with vomiting. Potassium depletion also gives rise to alkalosis as this appears to encourage the secretion of hydrogen ions by the distal renal tubules (pp. 580-581).

Consequences of Alkalosis. The sequence of events which occurs when hydrochloric acid is lost from the body as a result of vomiting is shown in Figure 21. The loss of hydrogen ions in severe and continuous vomiting lowers the hydrogen ion concentration of the blood and leads to alkalosis. The effect is mitigated by an increase in the ionisation of blood carbonic acid to hydrogen and bicarbonate ions, as indicated by the broad arrow. The former tends to restore the hydrogen ion concentration towards normal, and the latter replaces the chloride in the blood which has also been lost in the gastric contents. For as long as the chloride deficiency persists increased tubular conservation of bicarbonate sustains the alkalosis.

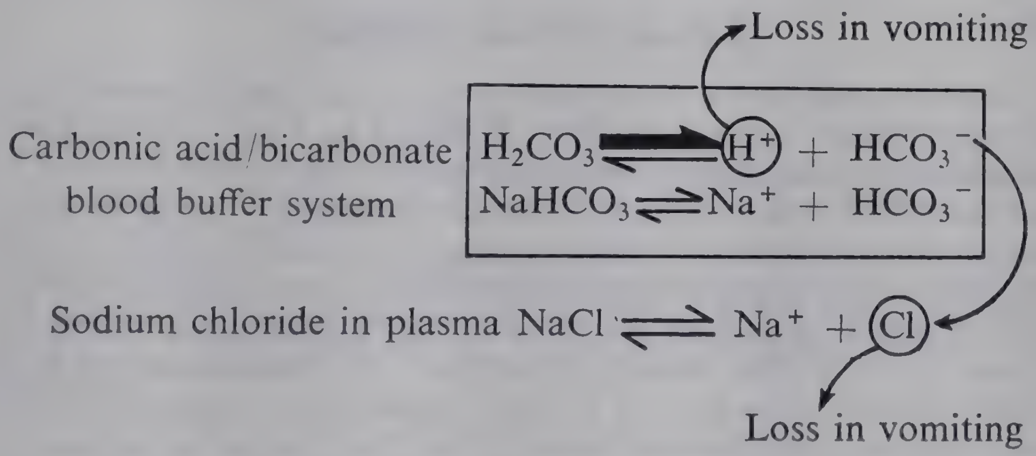

Loss in vomiting
Carbonic acid/bicarbonate blood buffer system
$H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$
$NaHCO_3 \rightleftharpoons Na^+ + HCO_3^-$
Sodium chloride in plasma $NaCl \rightleftharpoons Na^+ + Cl$
Loss in vomiting

FIG. 21 Carbonic acid/bicarbonate Blood Buffer System

Alkalosis of some duration is often associated with significant depression of renal function with uraemia. Protein and casts are found in the urine, and the diagnostic error of attributing vomiting due to pyloric stenosis to primary renal disease must be avoided. In spite of the existence of metabolic alkalosis, the urine may remain acid. There are two causes for this paradoxical aciduria. The alkalosis is frequently associated with chloride depletion, and under these circumstances an alkaline urine cannot be elaborated. Secondly, respiratory compensation for the alkalosis results in a rise in Pa_{CO_2} which is also known to increase renal tubular reabsorption of bicarbonate. Apathy, personality changes, delirium and stupor occur; since the patient usually suffers from associated water and potassium depletion, it is probably wrong to attribute these features solely to the effect of alkalosis. Tetany may occur spontaneously or be induced by the Trousseau manoeuvre and is due to a reduction in the concentration of plasma ionised calcium.

The diagnosis of alkalosis may be made with certainty only by estimation of the concentration of plasma bicarbonate. In moderately severe alkalosis this is elevated to 35 mEq/*l*. The pH of the blood is also elevated.

Treatment. In patients with mild or moderate alkalosis in whom the bicarbonate concentration is not elevated above 30 mEq/*l*, it is often possible to correct the abnormality by the intravenous administration of isotonic sodium chloride. This treatment is effective only if there is normal renal function. In this event the chloride is retained and excess bicarbonate in the plasma is excreted in the urine. Two to four litres may be required in the course of 24 hours. In severe cases the administration of ammonium chloride by intravenous infusion has been found effective and is conveniently prepared in a solution which is designed also to repair the commonly associated potassium deficit. This is called the 'gastric solution'. One litre of a solution containing 63 mEq/*l* of sodium chloride, 17 mEq/*l* of potassium chloride and 70 mEq/*l* of ammonium chloride may be given in four to six hours and repeated as indicated by blood analysis. The use of this solution is of particular benefit in these patients who are being prepared for operation for relief of gastric outlet obstruction (p. 468) and in whom repeated daily gastric lavage is needed to prevent vomiting and reduce the size of a dilated stomach.

Ketosis without Acidosis

The excessive production of β-hydroxybutyric acid and acetoacetic acid in diabetic ketoacidosis has already been described as a cause of acidosis. Abnormal amounts of acetoacetic acid also arise in the body when the carbohydrate in the food is inadequate and increased amounts of fat are being utilised for energy. This is commonly found in cases of cyclical or severe vomiting in children, severe vomiting of pregnancy, starvation, and in post-operative vomiting. Two opposing tendencies are obviously in operation, the ketosis tending to increase, and vomiting tending to decrease the concentration of hydrogen ions in the blood. In these cases it is not uncommon, therefore, to find that metabolic alkalosis coexists with ketosis. Thus, the presence of acetoacetic acid in the urine does not necessarily imply the existence of acidosis, and the existence of metabolic acidosis is established only by the determination of the blood pH or bicarbonate concentration.

Apart from the possible need to treat concomitant acidosis or electrolyte disturbances, ketosis is best remedied by restoring the consumption of carbohydrate to normal. In cases of diabetic ketosis the administration of insulin is essential. In the other forms of ketosis this need not be given. Ample supplies of glucose should be provided; if this cannot be taken by mouth an intravenous infusion of 5 per cent glucose in water may be given. Two to four litres of this solution may be needed in the course of the day.

Respiratory Acidosis and Alkalosis

Respiratory acidosis arises when the effective alveolar ventilation does not keep pace with the rate of production of carbon dioxide (p. 323). As a result the $Pa{CO_2}$ and carbonic acid concentration of the blood increase, and the pH falls. The distinction between respiratory acidosis and metabolic alkalosis is usually easily made from a knowledge of the cause of the disturbance. The reaction of the arterial blood is decisive; in both the $Pa{CO_2}$ is increased, but in respiratory acidosis pH is reduced, whereas in metabolic alkalosis the pH is increased. The kidney responds to an increase in Pa_{CO_2} by excreting an acid urine and conserving sodium bicarbonate. The causes and consequences of respiratory acidosis are given on page 323.

Respiratory alkalosis occurs when there is excessive loss of carbonic acid by over-ventilation of the lungs. Most commonly this occurs in hysterical over-breathing or in over-ventilation during the course of assisted respiration, though it may arise also in the course of meningitis, encephalitis, salicylate intoxication, and liver failure. Tetany may ensue.

Electrolyte repair solutions play no part in the treatment of respiratory acidosis or alkalosis, and therapy should be directed to the underlying disorder. The treatment of hypercapnia is described on page 332. Respiratory alkalosis due to hysterical overbreathing is best treated by giving 5 per cent carbon dioxide and oxygen, or by asking the patient to rebreathe his own carbon dioxide by breathing into a paper bag. Tetany may be treated by an intravenous injection of 10 ml of 10 per cent calcium gluconate if necessary. The underlying causative factors should receive appropriate attention.

J. S. ROBSON.

Further reading:

Black, D. A. K. (1967). *Essentials of Fluid Balance*, 4th ed. Oxford: Blackwell.

Lant, A. F. & Wilson, G. M. (1972). Diuretics, chap. 23 in *Renal Disease*. Ed. Black, D. A. K. Oxford: Blackwell.

Passmore, R. & Robson, J. S. *Companion to Medical Studies*, vol. I (1970), chaps 6 and 33; vol. II (1973), chap. 11, Vol. III (1974), chap. 49. Oxford: Blackwell.

Robinson, J. R. (1973). *Fundamentals of Acid-Base Regulation*, 4th ed. Oxford: Blackwell.

Diseases of the Cardiovascular System

Disorders of the heart and arteries are the major causes of disability and death in affluent countries today. More than 50 per cent of deaths in middle age and beyond can be attributed to the effects of high blood pressure and coronary and cerebral atherosclerosis. Other forms of heart disease are important as causes of ill health at earlier ages. Congenital heart disease predominates in infancy and childhood. Rheumatic fever is the main cause of heart disease in early adult life but its incidence is falling in contrast to the increase in ischaemic heart disease. Chronic bronchitis is an important cause of heart failure, particularly in industrial cities.

Diagnosis in heart disease can usually be made from a careful history and a detailed physical examination supplemented by radiography and electrocardiography; only occasionally is it necessary to make use of highly specialised techniques such as cardiac catheterisation and angiocardiography.

Patients with heart disease usually complain either of breathlessness, pain in the chest or swelling of the ankles. Other symptoms such as dizziness, faintness or palpitation are more commonly associated with an anxiety neurosis. It must not be forgotten that the symptoms which may arise in heart disease can also be produced by disorders in other systems. For example, breathlessness may be due to disease of the lungs, pain in the chest may be due to visceral or skeletal disease and oedema may be due to hypoproteinaemia. A careful appraisal of the history as regards capacity for familiar effort provides the best test of cardiac function.

Essentials in physical examination include a general inspection of the patient, palpation of the pulses, estimation of the arterial and venous pressures, assessment of heart size, auscultation of sounds and murmurs, and retinoscopy.

Radiology is of great value in diagnosis and in the assessment of cardiac enlargement and of the state of the pulmonary vasculature. Electrocardiography is important in the diagnosis of arrhythmias and myocardial infarction and is of great value in assessing the extent of cardiac involvement in rheumatic, hypertensive and other types of heart disease.

Therapeutic advances are being made particularly in the immediate management of myocardial infarction and in the field of cardiac surgery. As regards preventive cardiology, intensive study is being directed especially at the factors which may be responsible for coronary atherosclerosis.

PHYSICAL EXAMINATION

While taking the history and before proceeding to the examination of the heart, certain pertinent observations may be made. Many patients with heart disease appear to be in robust health. In contrast, those suffering from myocardial infarction may be distressed, sweating and cold, those with infective endocarditis may look pale and tired, and those with chronic cardiac failure may appear wasted.

Cyanosis depends on the absolute amount of reduced haemoglobin in the blood of the superficial vessels and is usually evident when this exceeds 5 g/100 ml; thus it is readily apparent in polycythaemia and cannot occur in severe anaemia even with extreme oxygen undersaturation.

Peripheral cyanosis is due to an excessive extraction of oxygen from the blood when the circulation is impaired from vasoconstriction, low cardiac output or stasis; it occurs in healthy people when they are cold, whereas warmth abolishes it.

Central cyanosis is due to oxygen undersaturation of the arterial blood from poor gaseous exchange in the lungs in such conditions as emphysema, pulmonary oedema and pneumonia or when there is a veno-arterial shunt in congenital heart disease. If the skin is warm and the tongue is cyanosed, it may be deduced that the cyanosis is central in origin. A combination of central and peripheral cyanosis may occur and is often seen in cardiac failure.

Anaemia may aggravate or precipitate angina or cardiac failure. In a patient with valvular disease it may be due to infective endocarditis.

Breathlessness may be observed at rest, especially if the patient is asked to lie flat. If it is of cardiac origin, it indicates pulmonary venous congestion or pulmonary oedema.

Obesity aggravates, or may entirely account for, breathlessness on exertion; it decreases exercise tolerance in patients with angina.

Loss of weight is a common sequel to chronic cardiac failure. Wasting is also a feature of thyrotoxicosis which, particularly in the elderly, may readily be overlooked as a cause of atrial fibrillation or cardiac failure.

The Hands. The temperature of the skin varies with the skin blood flow. In an equable temperature and with normal arteries the skin temperature usually reflects the cardiac output; thus with a low output the hands are usually cold; conversely, with a normal or high output they are usually warm.

Unduly moist palms suggest anxiety if they are cold, or thyrotoxicosis if they are warm. Clubbing of the fingers occurs in cyanotic congenital heart disease and in advanced infective endocarditis but is more often found in other conditions such as bronchogenic carcinoma. 'Splinter' haemorrhages may be present in infective endocarditis but are not diagnostic of this condition and may be due merely to trauma.

Examination of the Arterial Pulse

The radial pulse should be examined for rate, rhythm, volume, character of the pulse wave and condition of the vessel wall.

RATE

Bradycardia. A heart rate of less than 60 beats a minute may be physiological or due to heart block. Excessive administration of digitalis is a common cause.

Tachycardia. A heart rate of more than 100 beats a minute in an adult with regular rhythm may be due to emotion, thyrotoxicosis, fever, cardiac failure or to an ectopic rhythm, such as paroxysmal tachycardia.

RHYTHM

An irregular pulse is commonly due to sinus arrhythmia, ectopic beats or atrial fibrillation. The term pulse deficit signifies a difference between the heart rate as recorded by auscultation and the pulse rate as counted at the wrist. It is a feature of ectopic beats and of atrial fibrillation because in these disorders some heart beats fail to produce an appreciable stroke volume.

VOLUME

By pulse volume is meant the amplitude of expansile movement of the vessel wall during the passage of the pulse wave. The pulse volume provides a useful clinical estimate of the left ventricular output per beat (stroke volume). It is modified by vasomotor tone and local conditions such as a sclerotic or unusually small artery.

A pulse of small volume is characteristic of shock and of low output heart failure and may occur with severe valvular stenosis or severe pulmonary arterial obstruction. A pulse of large volume is found in fevers, aortic regurgitation, atherosclerosis of the aorta, extreme bradycardia as with heart block and in diseases in which there is an increased cardiac output, e.g. severe anaemia and thyrotoxicosis. If pulses are unequal, it can be inferred that there is a vascular block of which the most common causes are embolism, thrombosis and atherosclerotic obstruction.

CHARACTER OF THE PULSE WAVE

Anacrotic Pulse. In aortic stenosis a notch may sometimes be felt on the upstroke of the pulse, and the wave may be prolonged and of small amplitude.

Dicrotic Pulse. Accentuation of the dicrotic wave, sometimes so marked as to give the impression of a double pulse at the wrist, may be found in any condition with vasodilatation, e.g. high fever.

Collapsing Pulse. A characteristic pulse wave is felt at the wrist in severe aortic regurgitation. There is a sharp impact from the rapid filling and sudden rise of pressure associated with a large systolic discharge from the left ventricle and a rapid falling away or collapse from the subsequent sudden fall of pressure due to regurgitation of blood through the incompetent aortic valve. Such a pulse is frequently accompanied by capillary pulsation due to arteriolar dilatation. The diastolic pressure will be low or even zero. A high pulse pressure and bounding pulse may occur in any condition associated with vasodilatation, e.g. anaemia, fever or thyrotoxicosis.

Pulsus Alternans. The pulse is regular but the amplitude is larger and smaller in alternate beats. It is usually best detected with the sphygmomanometer; there may be a difference of 10-40 mm between strong and weak beats. It is a sign of left ventricular failure.

Pulsus Bisferiens. A pulse with a double peak is suggestive of combined aortic stenosis and regurgitation.

Pulsus Paradoxus. The normal increase in capacity of the pulmonary vascular bed which occurs during inspiration results in a diminished return of blood to the left side of the heart. Hence the volume of the pulse is decreased by inspiration. In pericarditis with effusion or in constrictive pericarditis the normal increase in venous return to the right side of the heart during inspiration cannot be accommodated. Hence there is an exaggerated fall in pulse volume. Pulsus paradoxus is also found in asthma and stridor, when there is an increased change in intrathoracic pressure with respiration.

Vessel Wall

The condition of the vessel wall of medium-sized arteries, such as the brachials, frequently shows evidence of arterial thickening, tortuosity and undue mobility. These changes signify medial sclerosis which, however, is not related to hypertension or narrowing of the lumen.

Lower Limb Pulses

In younger hypertensives and in children suspected of having congenital heart disease the femoral pulses should always be examined. Absence, weakness or delay after the radial, may be due to coarctation of the aorta, in which case the blood pressure in the lower limbs is reduced, in contrast to the raised pressure in the upper limbs.

In peripheral vascular disease, the pulses should be felt and compared in the femoral, popliteal, posterior tibial and dorsalis pedis vessels.

Arterial Pulsation in the Neck

Excessive arterial pulsation in the neck may be seen in aortic regurgitation, coarctation of the aorta or sometimes from kinking of the carotid artery, especially on the right, due to unfolding of an atheromatous aorta.

Examination of the Jugular Veins

The internal jugular veins reflect the pressure and pulsations of the right atrium and serve as convenient clinical manometers. Distension of external jugular veins is an unreliable index of right atrial pressure because kinking of these vessels may make the pressure appear falsely high. Venous pulsation can be distinguished from arterial pulsation by its characteristic wave-form and pressure and by its variation with posture, respiration and pressure on the abdomen and by the fact that arterial pulses are readily felt whereas venous pulsation is seldom palpable even when easily seen. Two positive waves, termed 'a' and 'v' (Fig. 22), can normally be seen in the venous pulse but to do so it may be necessary for the patient to be reclining at 30° or in the horizontal position. The top of the venous column does not normally exceed 2 cm vertically above the sternal angle with the patient reclining at 45°.

Increased venous pressure occurs as a result of cardiac failure, of pulmonary embolism or of pericardial effusion or constriction. Venous obstruction, e.g. by a mediastinal tumour compressing the superior vena cava, causes distension without pulsation and is not influenced by pressure over the abdomen.

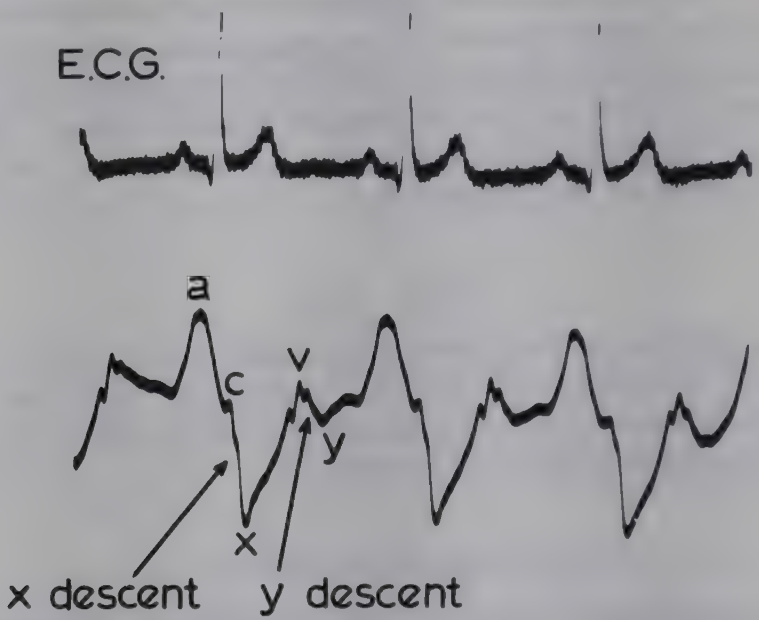


FIG. 22

FORM OF THE VENOUS PULSE WAVE

Examination of the jugular veins for the normal 'a' (atrial, presystolic) and 'v' (ventricular) waves may give useful information. In tricuspid stenosis, pulmonary stenosis and pulmonary hypertension from any cause the 'a' wave will be exaggerated because the atrium has to contract against increased resistance and in tricuspid regurgitation a positive, systolic wave will replace the usual dip in pressure in early systole due to regurgitation of blood into the atrium at this time.

Examination of the Heart

PALPATION OF THE PRECORDIUM

The *apex beat* may be defined as the furthest point of cardiac pulsation downwards and to the left at which the finger is distinctly lifted. It usually lies in the fifth left intercostal space within the midclavicular line. Its position is partly dependent on the shape and size of the chest, and its localisation may be difficult or impossible where there is obesity or emphysema. Displacement of the apex beat to the left is a reliable indication of cardiac enlargement provided that the possibility of displacement from other causes has been excluded—e.g. fibrosis or collapse of the left lung and pleural effusion on the right side. Scoliosis and cup-shaped depression of the sternum may cause displacement to the left.

On palpation, not only should the *position of the apex beat* be located as a guide to cardiac enlargement or displacement but the *quality of the impulse* should be noted. A heaving impulse at the apex is usually due to hypertrophy of the left ventricle. A central lift may be due to hypertrophy of the right ventricle or to systolic expansion of the left atrium from mitral regurgitation. A tapping impulse is due to closure of the mitral valve and corresponds in mechanism to the loud first heart sound. A forceful impulse may be felt in nervous individuals, but in practice there is rarely difficulty in differentiating this from the sustained heave which is characteristic of hypertrophy. *Thrills* frequently accompany loud murmurs from valvular or congenital heart disease. The most important are:

Mitral: Systolic—mitral regurgitation; diastolic—mitral stenosis.
Pulmonary: Systolic—pulmonary stenosis; patent ductus arteriosus.
Aortic: Systolic—aortic stenosis.
Lower Left Sternal Edge: Systolic—ventricular septal defect.

HEART SOUNDS AND MURMURS

Sounds. The first heart sound results from closure of the mitral and tricuspid valves. The second heart sound is due to closure of the aortic and pulmonary valves and marks the end of systole. Both heart sounds may be diminished in the presence of obesity or emphysema. Accentuation of the first sound at the apex may be present with mitral stenosis, emotion, thyrotoxicosis or hypertension. This sound may be diminished in mitral regurgitation, rheumatic carditis or in severe cardiac failure, or may largely be obscured by a loud systolic murmur. Accentuation of the aortic component of the second sound is found in hypertension, atherosclerosis and syphilitic aortitis. It may be diminished in aortic stenosis. The pulmonary component of the second sound may be accentuated in pulmonary hypertension, which is most often due to mitral stenosis, left ventricular failure, or congenital heart disease. It may be diminished in some cases of pulmonary stenosis.

SPLITTING OF THE FIRST SOUND. Splitting of the first heart sound, which is due to asynchronous closure of the mitral and tricuspid valves, is not uncommon in normal people. The two components have much the same quality and are separated from one another by a very short interval.

SPLITTING OF THE SECOND SOUND. Splitting of the second sound is due to slightly asynchronous closure of the aortic and pulmonary valves. Normally splitting can be recognised only during inspiration when the increased venous return prolongs the duration of right ventricular systole. The main importance of splitting lies in distinguishing it from one of the forms of triple rhythm and from the '*opening snap*' of the mitral valve. Wide splitting is a characteristic sign in atrial septal defect (p. 293).

OPENING SNAP. The opening snap immediately precedes the mid-diastolic murmur of mitral stenosis and is best heard at the lower, left sternal margin. This 'opening snap' should serve as a reminder to listen carefully for such a murmur.

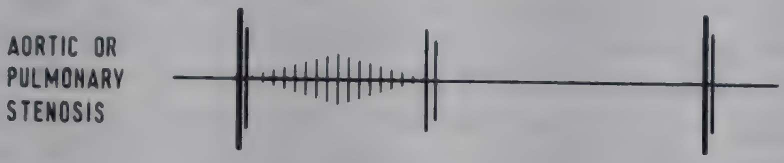
TRIPLE RHYTHM. Triple rhythm may be said to occur whenever three sounds can be heard instead of the normal two but it is customary to exclude the opening snap. An extra heart sound, in diastole, may be *physiological*, especially in children or young persons and in pregnancy, or *pathological* in failure of the left or right ventricle. The differentiation between a physiological and pathological triple rhythm cannot be made by auscultation alone, but only by the presence or absence of other evidence of heart disease, i.e. by consideration of the symptoms and signs and by the detection of some aetiological factor which might be responsible for cardiac failure (e.g. hypertension). One should always beware of drawing conclusions from an isolated sign. In established heart disease triple rhythm is usually of serious prognostic significance.

The extra sound may precede the normal first heart sound, when it is referred to as an atrial or fourth heart sound, or follow the normal second sound (when it is referred to as a ventricular filling or third heart sound). The extra sound is separated from the normal sound by a readily appreciable gap and has a different quality, being dull or muffled. The tachycardia which often accompanies cardiac failure makes precise timing difficult or impossible, and under these circumstances a characteristic cadence can often be heard to which the descriptive term *gallop rhythm* has been applied.

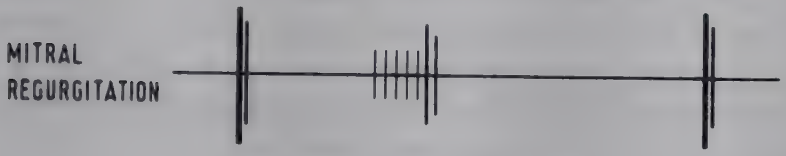
Murmurs. If a murmur is heard it is important to note the *intensity*, e.g. faint, moderate or loud; the *position of maximal intensity*; the *timing*, e.g. systolic or diastolic; the *quality*, e.g. blowing or harsh; the *pitch* and the direction in which it is *conducted*. Some murmurs are characteristic, e.g. the long pan-systolic murmur of mitral regurgitation, the shorter, harsher mid-systolic murmur of aortic or pulmonary stenosis, the harsh, crescendo pre-systolic murmur at the apex leading up to a sudden, loud first sound in mitral stenosis or the blowing early diastolic murmur of aortic regurgitation best heard down the left sternal border. It will be appreciated that in the presence of tachycardia it may be difficult to define the position of a murmur in diastole. In these circumstances interpretation of the murmur depends upon its other characteristics. Further details of heart murmurs are discussed under Valvular Heart Disease, pages 253-259, and are summarised in graphic form in Fig. 23.

BENIGN SYSTOLIC MURMURS. A systolic murmur may be heard in the absence of organic heart disease. Such murmurs are particularly common in the pulmonary area but may be heard at the apex or to the left of the lower sternum. Systolic murmurs not based on structural abnormalities in the heart are frequently heard in hyperkinetic states, e.g. anaemia, fever, thyrotoxicosis, pregnancy or tachycardia from any cause such as exercise or emotion.

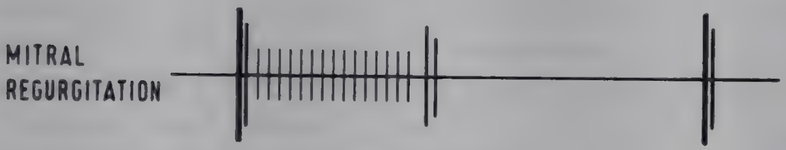
The louder or harsher the murmur, the more likely it is to be of pathological significance. A soft pulmonary systolic murmur in the absence of other abnormal signs can be ignored but an apical systolic murmur radiating to the axilla usually signifies mitral regurgitation. If a diastolic murmur can also be heard the systolic murmur is certainly due to organic disease. In cases of doubt the presence or absence of enlargement of the heart and great vessels must be determined and an electrocardiogram recorded. Particular attention should be paid to the size of the left atrium in the right oblique position (with barium in the oesophagus) because enlargement usually accompanies mitral valvular disease. In the absence of any other evidence of the commoner causes of organic systolic murmurs, i.e. rheumatic valvular disease and congenital defects, the murmur can be ignored and the patient reassured. No restrictions on activity are indicated.



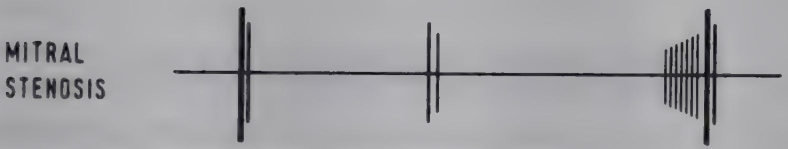
Mid-systolic murmur



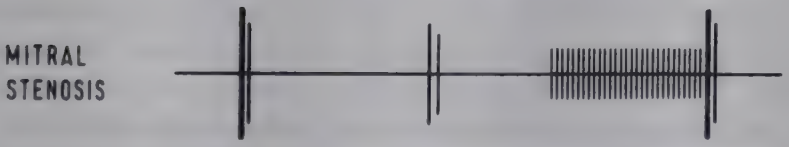
Late systolic murmur



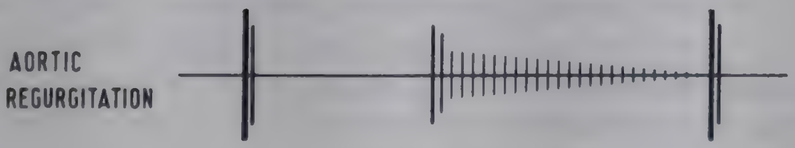
Pan-systolic murmur



Pre-systolic murmur



Mid-diastolic murmur



Early diastolic murmur

FIG. 23

HEART MURMURS

Examination for Signs of Cardiac Failure

The signs of cardiac failure are described on pages 244-247.

Estimation of the Blood Pressure

The blood pressure depends principally on the cardiac output and the peripheral resistance. The range of normal varies considerably not only with age but from patient to patient and from time to time and with the circumference of the arm in relation to the width of the cuff. The blood pressure varies greatly with exercise and emotion, and to a slight extent with meals and smoking. Casual readings in the consulting room or outpatient department may be very different from resting readings taken in bed after a night's sleep, reassurance and repeated recordings on different occasions. The information to be gained from a single reading is limited. There is some difference of opinion as to what level constitutes hypertension. A consistent level of 150/90 in young people is suspicious and a pressure of 160/95 should be regarded as abnormal.

It is important to distinguish predominantly systolic from diastolic hypertension. Emotion chiefly affects the systolic pressure. Systolic hypertension is also found in elderly patients with atherosclerosis of the aorta (and hence loss of elasticity) and in aortic regurgitation, heart block and thyrotoxicosis. It is of less significance in prognosis than diastolic hypertension which largely depends on constriction of the arterioles and is most commonly associated with essential hypertension, renal disease and toxaemia of pregnancy.

PULSE PRESSURE. The pulse pressure is the difference between the systolic and diastolic pressure. In hypertension the pulse pressure is commonly increased (e.g. 220/120), particularly if there is atherosclerosis of the aorta (e.g. 200/95). It is often raised in thyrotoxicosis, and in aortic regurgitation it may be very large (e.g. 200/40). In aortic stenosis it is characteristically small (e.g. 110/90).

ELECTROCARDIOGRAPHY

Electrocardiography plays an important part in the diagnosis and investigation of heart disease. Its main value lies in the elucidation of cardiac arrhythmias (p. 225) and conduction defects (p. 235), and in the diagnosis and location of myocardial infarction; it is of particular value in cases of unexplained chest pain or collapse. Electrocardiograms must always be interpreted in the light of the entire clinical picture. For instance, digitalis and quinidine, myxoedema, and certain electrolyte disturbances cause electrocardiographic changes which may easily be misinterpreted. The electrocardiogram (ECG) is the graphic representation of the electrical changes that take place in cardiac muscle cells and which precede contraction of the muscle fibre. The waves which are seen in the ECG can be understood in relation to the changes which occur during stimulation of a single muscle strip.

In its resting condition, a cell is in a state of electrical balance. When a cell is stimulated at one end, the activation process spreads rapidly through the strip, and for a very short time a potential difference exists between that part of the strip which has been activated and the part which is still in its resting state. This transient potential difference can be detected by a galvanometer, which will show a deflection. The P wave and QRS complex of an ECG correspond to this deflection as it occurs in atrial and ventricular muscle respectively. As the impulse spreads through the cell, contraction occurs, and after a short interval a recovery process takes place, restoring electrical balance. The T wave corresponds to this recovery process in the ventricle.

If the passage of an impulse along a strip of heart muscle is recorded by a unipolar lead, the deflections of the galvanometer, and hence the waves of the ECG, will vary according to the position of the exploring electrode in relation to the muscle strip (Fig. 24). When the impulse moves towards the electrode, a positive wave (R) is recorded. When the impulse moves away from the electrode, a negative wave (Q or S) is recorded.

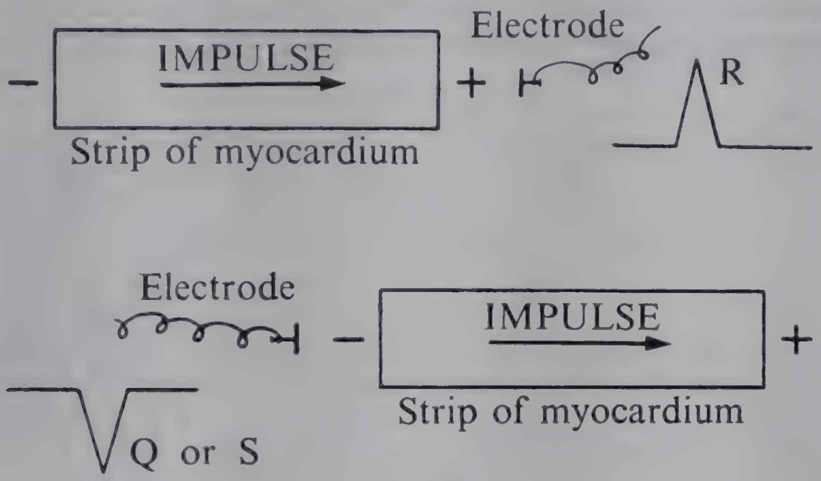


FIG. 24

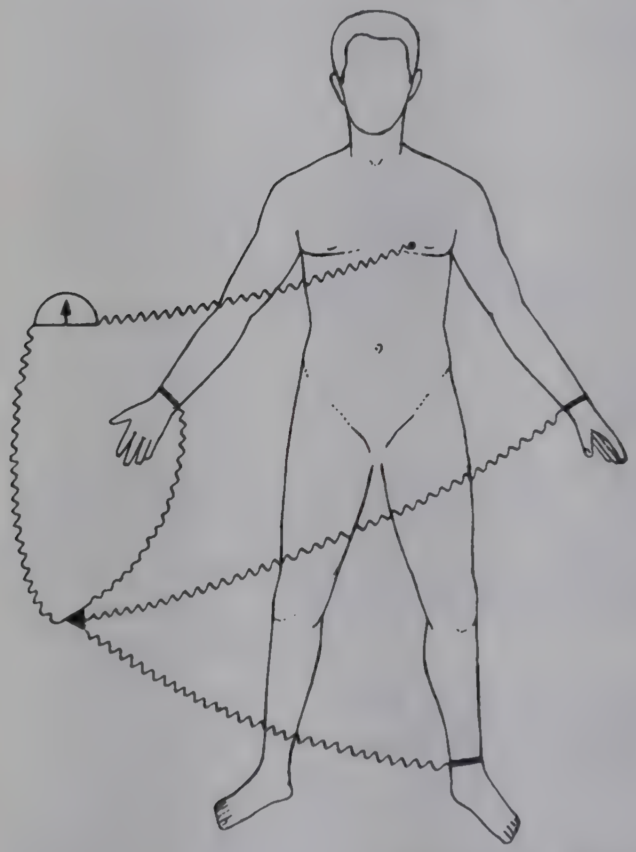
The electrocardiograph consists of a galvanometer and two metal plates (electrodes) which are attached to two points on the body surface. The resulting tracing is termed a 'lead' A bipolar lead measures the difference of potential between two sites on the body surface Three such bipolar leads are used, the electrodes being placed as follows:

Lead I	left arm—right arm
Lead II	left leg—right arm
Lead III	left leg—left arm

Unipolar leads give more accurate information about the state of the myocardium because they measure the actual potential at a given site, the second electrode being made of zero potential by an electrical device.

The use of unipolar leads is based on Einthoven's hypothesis that the heart may be considered to lie at the centre of an equilateral triangle, the angles of which are at the right arm, the left arm and the left leg, and that the algebraic sum of the potential differences between these three points at any instant is zero. If these points are connected they constitute the 'central' terminal. This is connected to one pole of the galvanometer, and the other pole is then connected to an electrode which can be placed anywhere on the body surface, and which is termed the exploring electrode. Such an electrode detects the electrical events of the heart as if it were situated on that part of the heart to which it lies closest. Tracings obtained in this way are termed V leads, and usually these are recorded from nine positions—the right arm (VR), the left arm (VL), the left leg (VF), and six positions on the chest wall (V_1-V_6) (Fig. 25). The amplitude of the unipolar limb leads is 'augmented' by removing the contribution to the 'central terminal' of the limb where the exploring electrode is; the leads are then termed aVR, aVL and aVF.

An example of a single lead of an ECG is shown in Figure 26. The letters P. Q, R, S and T were applied to the various waves many years ago by Einthoven. The P wave represents the passage of the activating impulse through the atria. The QRS complex represents the passage of the activating impulse through the ventricles, Q being applied to an initial negative deflection. R to the first positive deflection whether preceded by a Q wave or not, and S to a negative deflection following an R wave. The PR interval is measured from the start of the P wave to the start of the ventricular complex, i.e. if a Q wave is present, it is strictly speaking the PQ interval. The T wave represents ventricular recovery. The ST segment extends from the end of the QRS complex to the commencement of the T wave. The heavy vertical lines on the paper, on which the ECG is recorded, are 0·2 seconds apart and the fine vertical lines are 0·04 seconds apart. The approximate rate of the heart per minute can be calculated when regular by dividing 1,500 by the number of fine divisions between two successive corresponding points on the electrocardiogram, e.g. the peaks of the R waves. If the rhythm is irregular the number of QRS complexes in 3 seconds can be multiplied by 20.



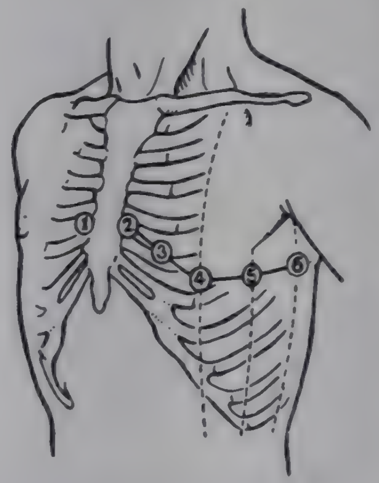


Fig. 25

Positions of Exploring Electrode

Unipolar chest leads V_1-V_6.

The principal deviations from the ECG of a normal person (Fig. 27) will now be considered in more detail.

P Wave

ABNORMALITIES OF P WAVES. Prominent P waves may occur in atrial hypertrophy, being broad and bifid in the left atrial hypertrophy of mitral stenosis, and tall and peaked in the right atrial hypertrophy which accompanies tricuspid stenosis or right ventricular hypertrophy from pulmonary stenosis or pulmonary hypertension.

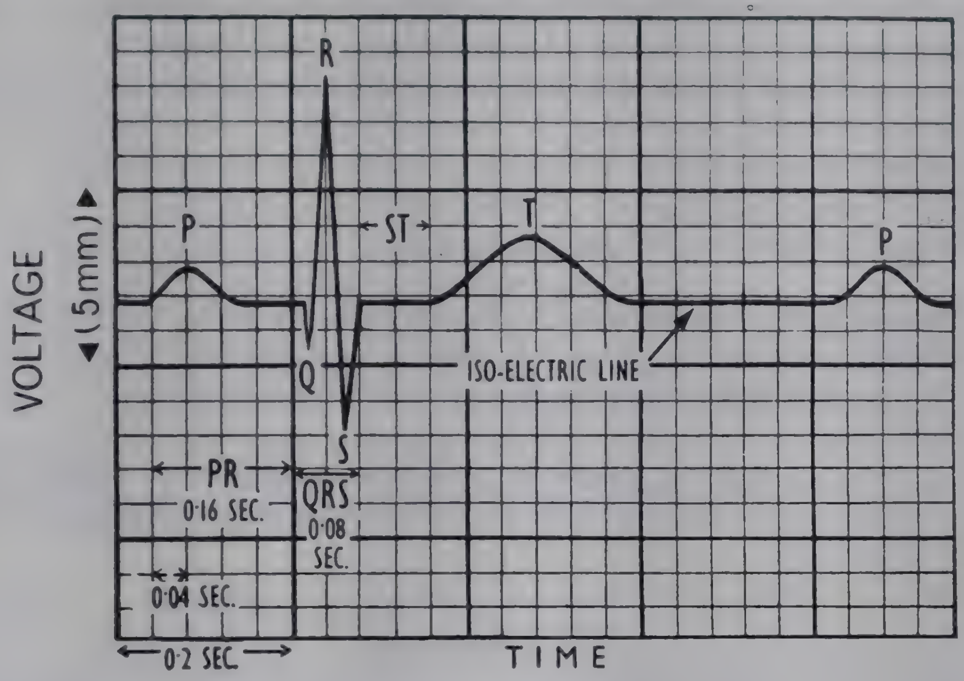


FIG. 26

THE BASIC FEATURES OF AN ELECTROCARDIOGRAM

The P wave tends to be of abnormal form if the activating impulse originates at some point in the atria other than the sino-atrial node. This occurs in supraventricular ectopic beats and in supraventricular paroxysmal tachycardia (Fig. 44, p. 232). In the latter, the P waves may be superimposed on the preceding T waves, and hence it may not be possible to identify them. Occasionally regular impulses originate in or near the atrio-ventricular node and travel backwards through the atria, as well as forwards to the ventricles, and this is termed nodal or junctional rhythm; in this condition the P waves tend to be

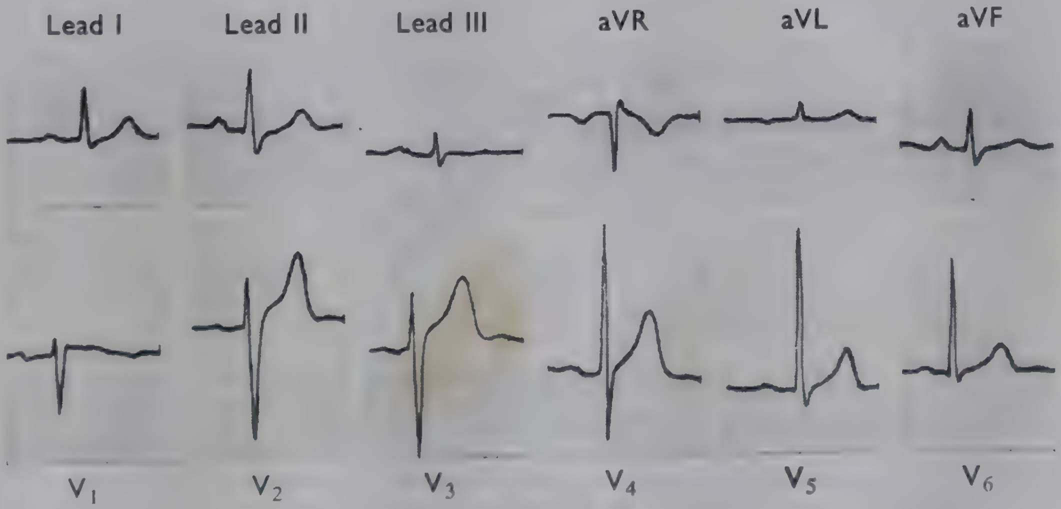


FIG. 27

NORMAL ELECTROCARDIOGRAM

inverted, and they occur before or after the ventricular complexes, or coincide with them and hence are hidden. Another condition, in which the P waves and ventricular complexes may coincide from time to time, is complete heart block, where the atria and ventricles beat independently of one another.

P waves are absent in atrial fibrillation and flutter, their place being taken by fibrillary 'f' (Fig. 42), or flutter 'F' waves (Fig. 43). Disturbances of rhythm are considered on page 225.

P-R INTERVAL

This represents the time interval from the moment when the impulse leaves the sino-atrial node until the moment when it starts to activate the ventricular muscle. The normal P-R interval is less than 0·21 of a second.

PROLONGATION OF THE P-R INTERVAL, and intermittent or complete failure of atrio-ventricular conduction (p. 235), constitute varying degrees of heart block (Figs. 47, 48 and 49).

QRS COMPLEX

The first part of ventricular muscle to be activated is the septum, and this activation occurs from the left bundle branch (Fig. 28). Subsequently, the impulse spreads out simultaneously through both ventricles from endocardial to epicardial surfaces. The amplitude and the duration of the QRS complexes depend to some extent on the bulk of muscle tissue through which the impulse is passing; as the left ventricle is normally much thicker than the right, most of the QRS complex is due to activation of the left ventricle.

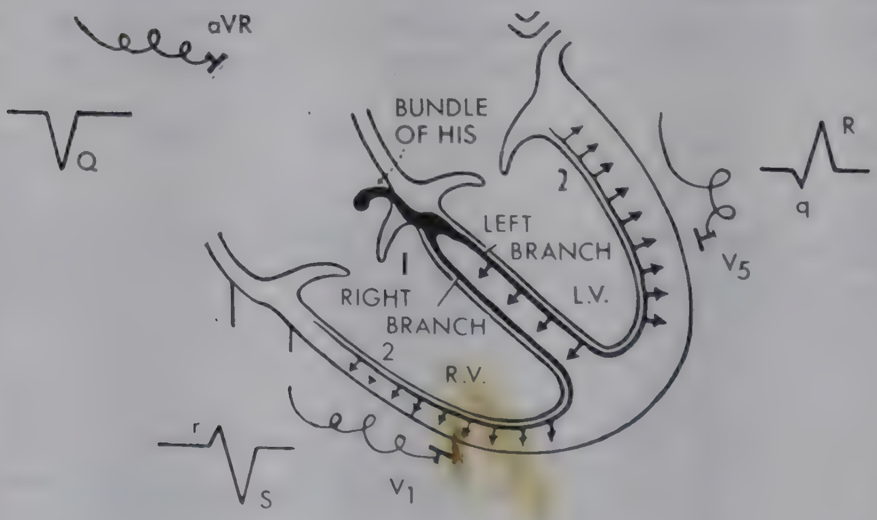


FIG. 28

First (1), the septum is activated from left to right. Secondly (2), the two ventricles are activated simultaneously but the L.V. is thicker and a larger current is generated.

This can be illustrated by consideration of two unipolar chest leads, one (e.g. V_1) lying over the surface of the right ventricle and the other (e.g. V_5) lying over the surface of the left ventricle (Fig. 28). In both these leads the initial wave (small r in V_1 and small q in V_5) is due to the same activation of the septum from left to right, and the subsequent wave (S in V_1 and R in V_5) is due to the spread of the same impulse through the left ventricle. A lead taken with an electrode which faces the cavities of the ventricles (aVR) shows a negative wave (deep Q) because the impulse is moving away from the electrode.

There is considerable individual variation in the pattern of the QRS complexes of the 12-lead ECG in normal people. This is partly related to variation in the anatomical position of the heart; for example, a longitudinal heart gives a different ECG from a broad, transverse heart.

ABNORMALITIES OF THE QRS COMPLEX. 1. *Ventricular Hypertrophy.* In left ventricular hypertrophy there is a greater preponderance than usual of the left ventricle over the right ventricle, with the result that the R waves in the left chest leads (V_5, V_6) and the S waves in the right chest leads (V_1, V_2) are of greater amplitude than usual (Fig. 29).

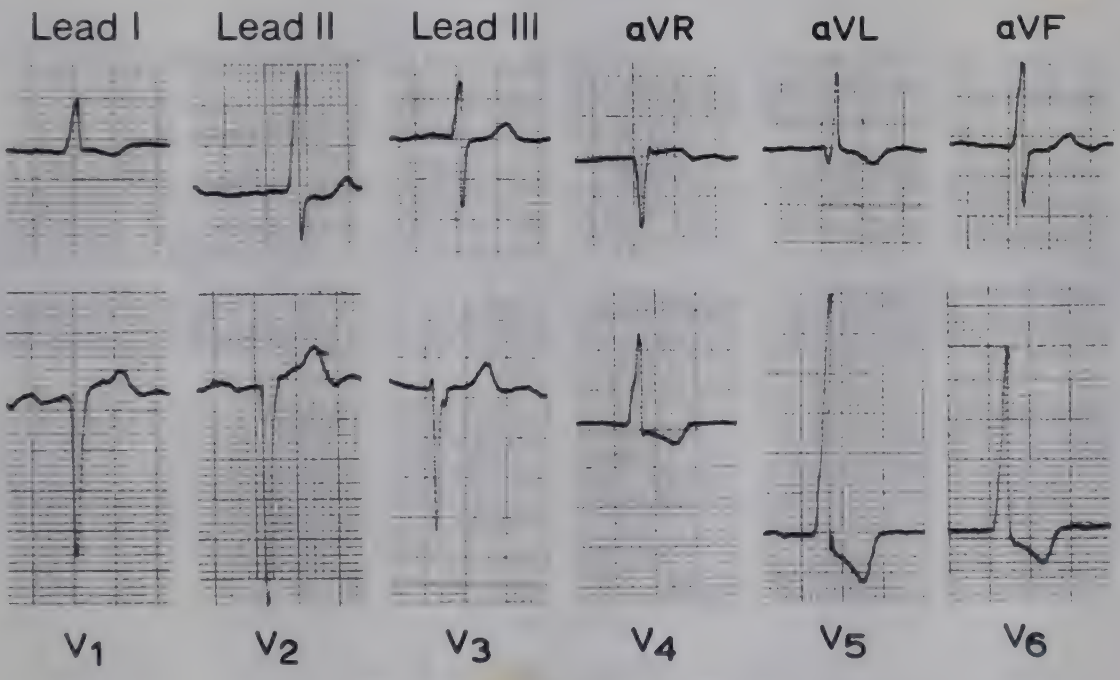


Fig. 29

LEFT VENTRICULAR HYPERTROPHY

Note: (1) tall R waves over left ventricle (V_{5-6});
(2) deep S waves over right ventricle (V_{1-2});
(3) depression and asymmetrical inversion of T wave in leads I, aVL, and V_4-V_6.

In right ventricular hypertrophy the wall of the right ventricle is thicker than usual though still less thick than the wall of a normal left ventricle, so that activation of the right ventricle is no longer overshadowed by activation of the left ventricle; it therefore causes changes in the ECG of which a prominent R wave in V_1 is the most important (Fig. 30).

2. *Bundle Branch Block.* This may be partial or complete, and may involve either the right or left branch of the bundle. Conduction of the activating impulse has to occur by unusual routes, and this leads to a prolongation of

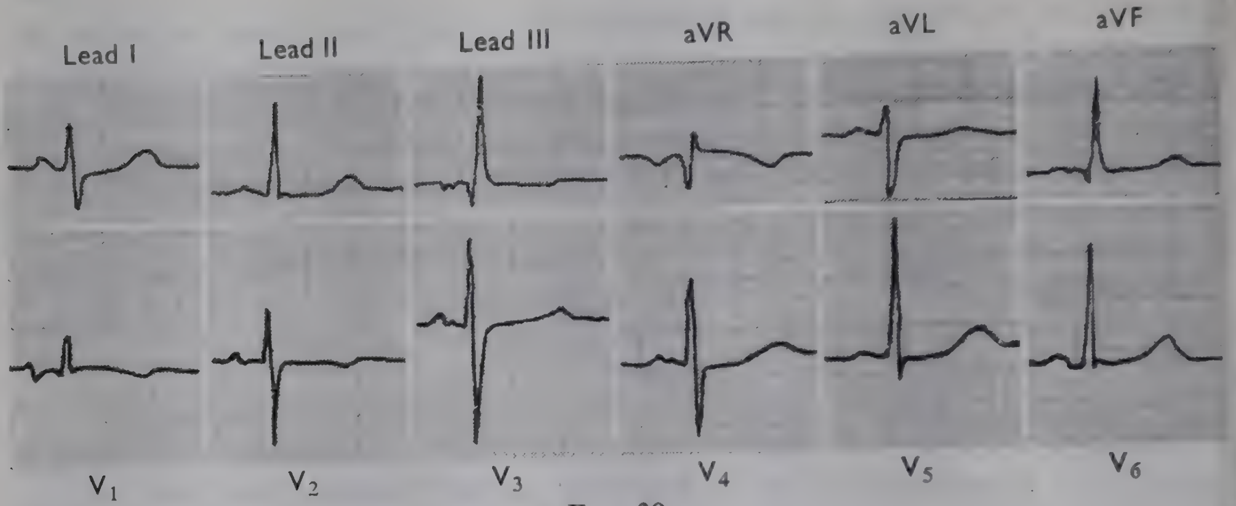


FIG. 30

RIGHT VENTRICULAR HYPERTROPHY

Note: (1) R wave exceeds the S wave in amplitude in V_1;
(2) inverted T waves in V_1 and V_2.

the conduction time, seen as a widening of the QRS complex, and to distortion of the normal pattern (Figs 31 and 32).

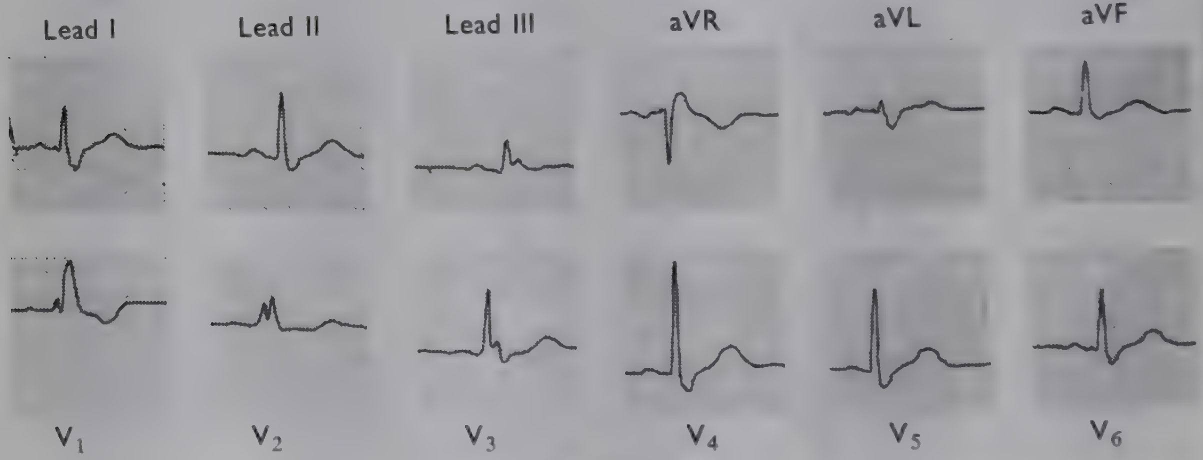


FIG. 31

RIGHT BUNDLE BRANCH BLOCK

Note: (1) wide QRS complexes in all leads;
(2) delayed peak of the main upright wave in V_1;
(3) slurred S waves in leads I, aVL, V_3-V_6;
(4) inverted T wave in V_1.

These features are due to the delay in activation of the right ventricle.

3. *Myocardial Infarction.* As a rule myocardial infarction occurs in the wall of the left ventricle and in the interventricular septum; the wall of the right ventricle is usually only affected in areas adjacent to a large septal infarct, and infarction of this wall can seldom be diagnosed electrocardiographically.

The electrocardiographic changes of myocardial ischaemia and infarction depend on the site, extent, severity and age of the damage. In myocardial infarction dead tissue, which cannot be activated but can still conduct impulses, acts as a hole or window in the myocardium. An overlying electrode therefore

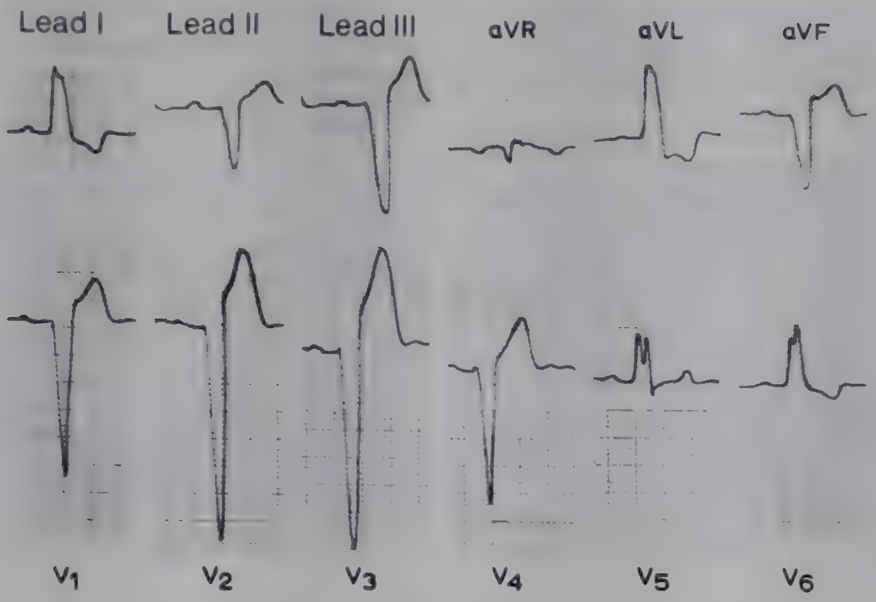


FIG. 32

LEFT BUNDLE BRANCH BLOCK

Note: (1) wide QRS complexes in all leads;
(2) delayed peaks of the broad, slurred R waves in leads, I, aVL, V_5 and V_6;
(3) inverted T waves in leads, I, aVL, V_5 and V_6.

These features are due to the delay in activation of the left ventricle.

reflects the electrical events which are occurring in the septum and the opposite wall of the heart. This is shown in the electrocardiogram as a negative wave (deep Q) for the reasons explained above (Figs. 33, 34 and 35B).

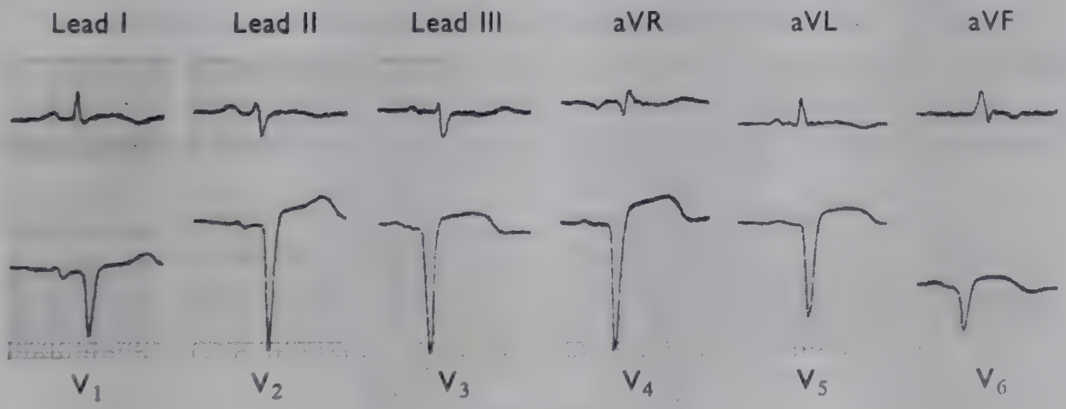


FIG. 33

ANTERIOR MYOCARDIAL INFARCTION

Note: (1) deep abnormal Q waves in V_1-V_6;
(2) S-T elevation in V_3-V_6 (elevation in V_1 and V_2 could be normal);
(3) shallow inverted T waves in I, II, aVL and V_6.

S-T SEGMENT AND T WAVE

The S-T segment represents the period when activation of the ventricles is complete, but before recovery has started. It should be iso-electric, i.e. it should not deviate from the base line.

The T wave represents repolarisation of the ventricular muscle. It should normally be upright in all leads except aVR, and sometimes leads III, and V_1.

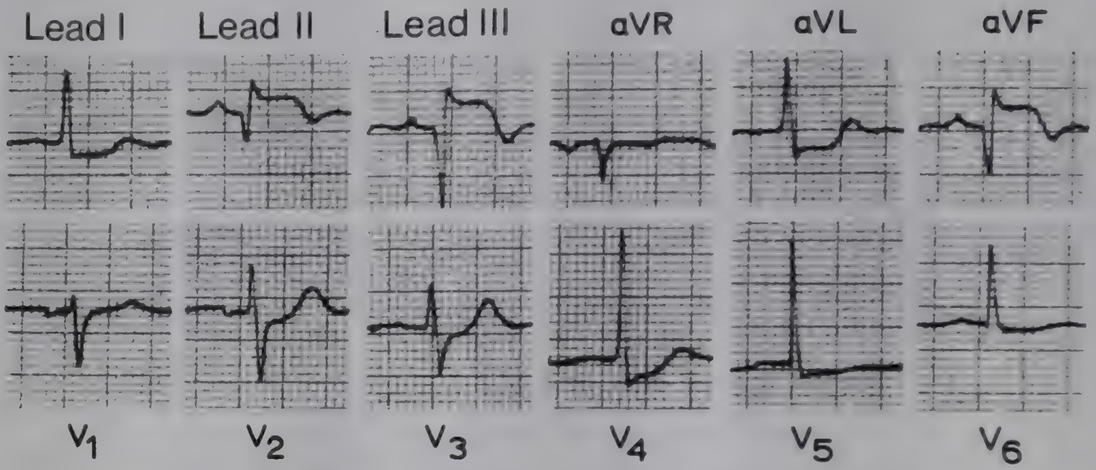


FIG. 34

INFERIOR MYOCARDIAL INFARCTION

Note: (1) deep abnormal Q waves in leads II, III and aVF;
(2) S-T elevation in leads II, III and aVF;
(3) inverted T waves in leads II and III and aVF;
(4) 'reciprocal' S-T depression in leads I, aVL and V_2-V_4.

ABNORMALITIES OF S-T SEGMENT AND T WAVE. This part of the electrocardiogram is altered by many factors. Among these are drugs (e.g. digitalis), disturbances of electrolyte balance (especially potassium), certain endocrine diseases (e.g. myxoedema) and—most important of all—myocardial ischaemia with or without subsequent infarction. The S-T segment and the T wave are also affected by primary myocardial disease, such as myocarditis or cardiomyopathy.

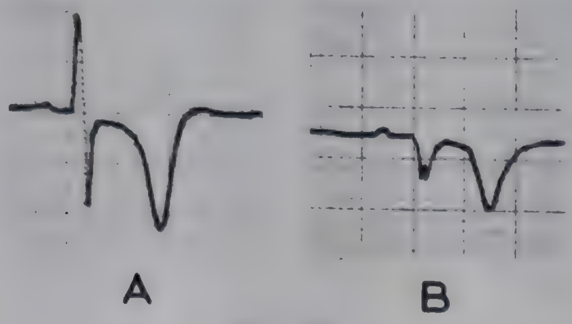


FIG. 35

MYOCARDIAL INFARCTION

Note: Symmetrical inversion of T wave with (A) normal QRS and (B) QS complex.

Ischaemia causes a change in the electrical state of the affected area of the myocardium, and this results in elevation or depression of the S-T segment, depending on which part of the myocardium is mainly involved, and also on the position of the exploring electrode. In angina there is usually S-T depression from subendocardial ischaemia. In myocardial infarction there is first S-T elevation with upward convexity and later inversion of T.

In acute pericarditis widespread S-T elevation occurs with upward concavity and later inversion of T because of the diffuse subepicardial damage. S-T depression is seen in gross ventricular hypertrophy, in bundle branch block (Figs. 31 and 32) and in ectopic beats.

A characteristically symmetrical inversion of the T wave is seen in myocardial infarction (Fig. 33) and usually follows displacement of the S-T segment within a period of a few hours or several days. Thereafter the T wave often gradually returns to normal, but may remain permanently inverted.

By means of these ST-T wave changes, the age of a myocardial infarct can often be assessed, and serial electrocardiograms are particularly valuable in this respect.

The preceding account of electrocardiography is greatly simplified, and details have not been given of the many normal variants which may be encountered, nor of the minutiae of diagnostic criteria. For a fuller account, reference should be made to a standard book on electrocardiography (p. 311). It is emphasised that while some understanding of electrocardiography is of value to all students and practitioners of medicine, interpretation of electrocardiograms should be made by physicians experienced in this field.

OTHER INVESTIGATIVE PROCEDURES

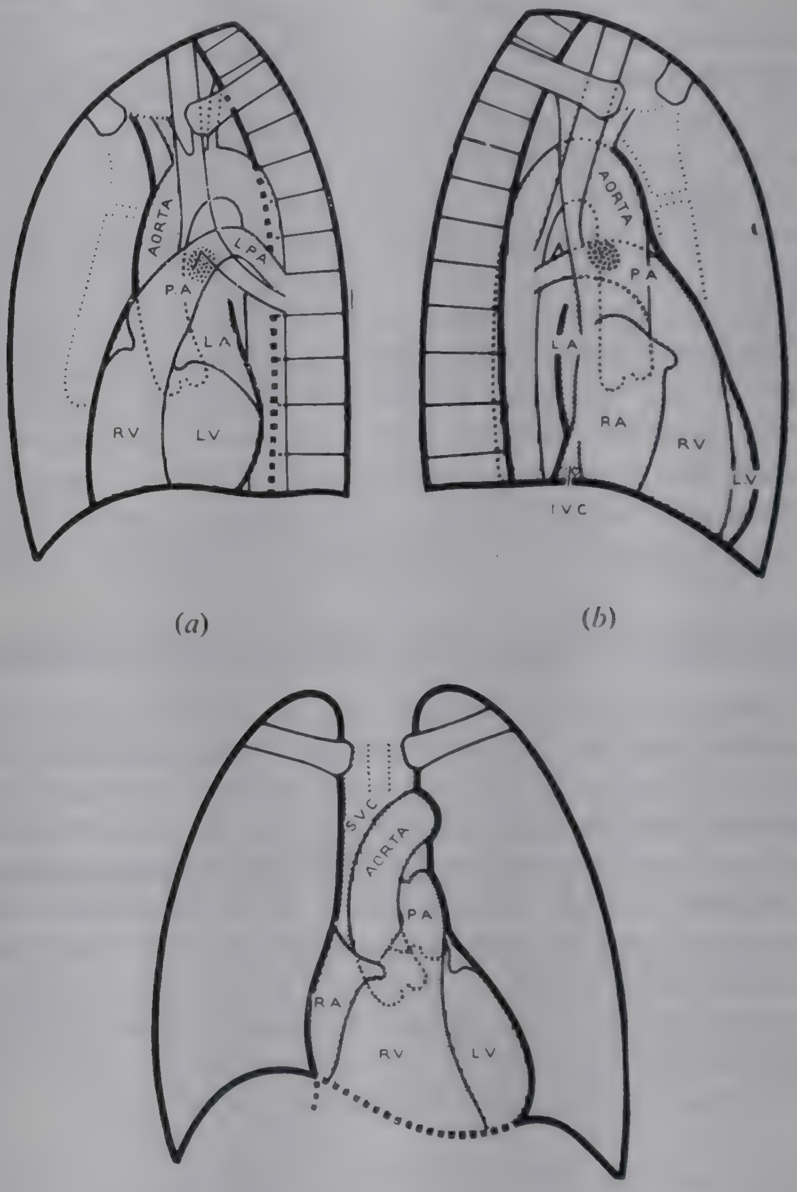
Radiology. The position of the apex beat as determined by palpation gives a rough estimate of cardiac size, but radiological examination is indispensable for accurate determination of the size and shape of the heart; it enables not only the width but also the depth of the heart to be seen. Individual chambers and the great vessels can also be studied (Fig. 36). Characteristic configurations are often to be seen in the various forms of valvular and congenital heart disease, in syphilitic aortitis and in aneurysm of the heart and aorta. The presence or absence of valvular calcification can also be determined. The oesophagus can be outlined by giving the patient some barium emulsion to swallow and any backward enlargement of the left atrium in mitral disease can be demonstrated. Serial radiographs provide a useful record of the patient's progress.

The lung fields can also be studied. Congestion and oedema can often be shown radiologically before they can be detected clinically. Congestion is first revealed by dilated pulmonary veins; oedema by thickened septa and dilated lymphatic vessels which result in horizontal lines in the costophrenic angles. More advanced changes are a hazy opacification in the hilar region and beyond, and pleural effusion.

Radioscopy. Screening of the heart, preferably with the aid of an image intensifier is of value in the detection of abnormal pulsations and of calcification.

ANGIOCARDIOGRAPHY. The individual chambers of the heart and the great vessels may be visualised by the injection of a radio-opaque material into a vein or by catheter directly into the aorta and heart before making a series of radiographs in rapid succession. Such studies are very useful in the differentiation of various congenital cardiac lesions and of vascular from other abnormal mediastinal shadows.

Phonocardiography. The phonocardiograph records heart sounds and murmurs and may help to elucidate difficult problems of auscultation. It is however no substitute for auscultation.



(*a*) (*b*)

(*c*)

FIG. 36

RADIOLOGICAL ANATOMY OF THE HEART

(*a*) Left oblique view. (*b*) Right oblique view. (*c*) Anterior view.

Echocardiography. High-frequency sound waves are reflected when they encounter the interface between solids and liquids. This principle is used in echocardiography in which reflected waves are detected and amplified. This technique is useful in the diagnosis of pericardial effusion and the study of movements of the mitral valve.

Cardiac Catheterisation. A radio-opaque catheter can be passed from a vein into the right atrium, right ventricle and pulmonary artery; its tip can be wedged in a small pulmonary artery and thus a record of the 'pulmonary capillary' or 'indirect left atrial pressure' can be obtained. A catheter may also be advanced from an artery into the aorta or left ventricle. If necessary the left atrium or left ventricle can be punctured with a needle. The pressures in these chambers can be recorded and the oxygen saturation of extracted blood samples estimated. Valuable information may be obtained in cases of congenital heart disease and in certain types of acquired heart disease. For example, in pulmonary hypertension the pressure in the pulmonary artery and right ventricle is increased; in pulmonary stenosis the systolic pressure is higher in the right ventricle than in the pulmonary artery; in aortic stenosis it is higher in the left ventricle than in the aorta. In atrial septal defect, because of the left to right shunt, the oxygen content of the blood in the right atrium is higher than that in the venae cavae; in ventricular septal defect the oxygen content of the blood in the right ventricle is higher than that in the right atrium.

If the oxygen content of blood from the pulmonary artery and brachial artery and also the oxygen consumption are known, then the cardiac output can be calculated from the Fick formula.

$$\text{Cardiac output} = \frac{\text{oxygen consumption}}{\text{arteriovenous oxygen difference}}$$

The area of a valve can be calculated if the pressure difference across it, and the cardiac output, are known. Likewise the volume of a shunt can be calculated from measurement of the relevant oxygen saturations.

Dye Dilution Curves. By the injection of a known quantity of a dye into a vein or directly into the heart through a catheter and estimation of its concentration in an artery, the presence of a shunt can be detected and the cardiac output measured.

DISORDERS OF CARDIAC RHYTHM AND CONDUCTION

Anatomy and Physiology

The impulse initiating cardiac contraction originates in the sinoatrial (S-A) node which lies at the junction of the superior vena cava and the right atrium. From the S-A node the impulse spreads through the atria to the atrio-ventricular (A-V) node at the base of the interatrial septum, and from there it is conducted down the A-V bundle to the ventricles. This bundle of specialised conducting tissue divides into right and left branches which pass down on either side of the interventricular septum and ramify widely beneath the endocardium in a syncytial network which then extends outwards towards the pericardium (Fig. 28, p. 218). The A-V node and bundle have a special blood supply from a branch of the right coronary artery, and hence localised vascular disease may cause serious impairment of its nutrition.

The inherent rhythm of cardiac contraction is under the influence of the autonomic nervous system and may be affected by emotion, various vagal and sympathetic reflexes, or by chemical substances, e.g. acetylcholine and catecholamines. The normal pacemaker of the heart, the S-A node, has an inherent rate of between 60 and 90/min but if it is depressed for any reason, e.g. by ischaemia or reflex vagal stimulation, the A-V node takes over control and initiates the impulse. The ventricles may develop an inherent rhythm if stimuli from the S-A and A-V nodes fail to reach them (as in complete heart block when the rate is usually 30 to 40/min).

The normal resting heart rate in adults varies between 60 and 90 beats per minute. It gradually slows from 120 to 140 in infants to about 80 at puberty.

Sinus Rhythms

SINUS BRADYCARDIA. The impulse originates in the S-A node but the rate is less than 60 beats per minute. Sinus bradycardia may occur in health from predominance of vagal tone and is common in athletes. There are usually no associated symptoms and the electrocardiogram is normal (Fig. 37). It may occur pathologically, e.g. in convalescence from infectious fevers, raised intracranial pressure, myxoedema, jaundice, excessive dosage with digitalis and acute myocardial infarction. Extreme sinus bradycardia may cause syncope. The term 'sick sinus syndrome' is sometimes used to describe depressed function of the S-A node which may be associated with atrial tachycardias.

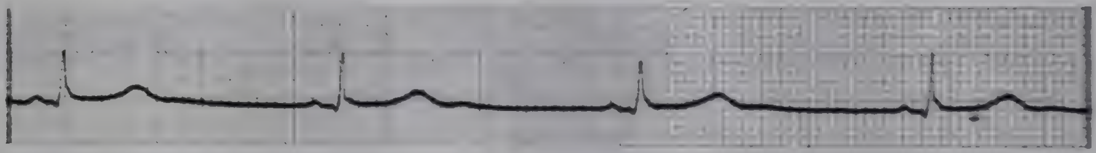


FIG. 37

SINUS BRADYCARDIA

Rate 50. Normal ECG.

($\frac{1}{2}$ mm ST elevation is within the normal range.)

SINUS TACHYCARDIA. The impulse originates in the S-A node but the rate is greater than 100 (adults). Sinus tachycardia may be associated with exercise or emotion or it may accompany fever, thyrotoxicosis, shock, acute haemorrhage, constrictive pericarditis or cardiac failure. The rate rarely exceeds 160 beats per minute and the electrocardiogram is otherwise normal (Fig. 38).

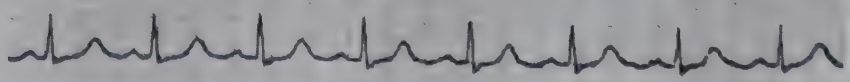


FIG. 38

SINUS TACHYCARDIA

Rate 110. Normal ECG.

SINUS ARRHYTHMIA. The impulse originates in the S-A node but the rhythm is irregular. The heart rate increases in inspiration and slows in expiration. Hence deep breathing may help in its differentiation from other arrhythmias. This rhythm is of no pathological significance and is most commonly seen in the young. The electrocardiogram shows rhythmic variations in the length of the cardiac cycles but is otherwise normal (Fig. 39).

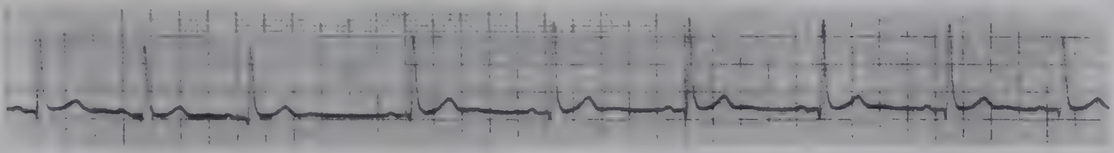


FIG. 39

SINUS ARRHYTHMIA

Note varying intervals between ventricular complexes. Normal ECG.

Ectopic Rhythms

When the impulse arises elsewhere than in the S-A node, e.g. in atria, A-V node or ventricles, it is referred to as an ectopic rhythm and may be regular or irregular.

1. Ectopic beats (Extrasystoles)

Ectopic beats arise from some abnormal focus in the heart and are really premature beats coming earlier than expected in the cardiac cycle. The term extrasystole is really a misnomer because, except in rare instances, there is in fact no 'extra' or additional beat. Since the heart muscle is rendered refractory by the ectopic beat, the next impulse from the S-A node usually fails to excite the ventricles and there is a long (compensatory) pause with increased diastolic filling so that the next normal contraction is augmented. The site of origin may be in the atria, ventricles or occasionally in the A-V node and can be recognised only by means of an electrocardiogram (Figs. 40 and 41).

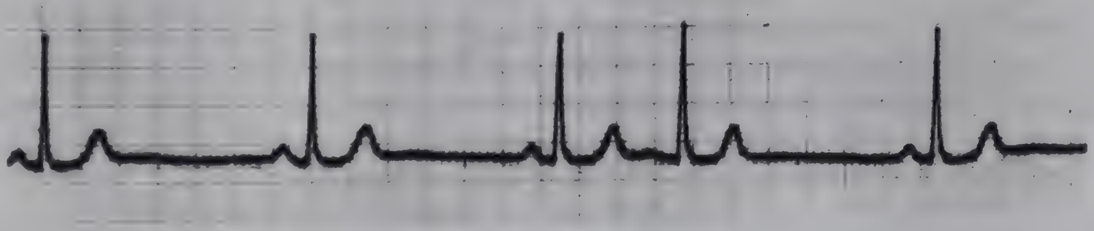


FIG. 40

SUPRAVENTRICULAR ECTOPIC BEATS

The fourth beat is premature; the P wave is abnormal but the QRS is unchanged.

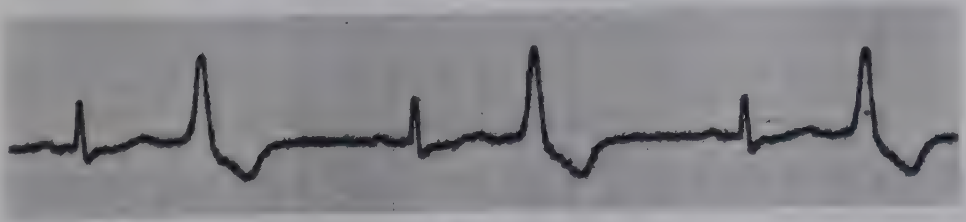


FIG. 41

VENTRICULAR ECTOPIC BEATS

The first, third and fifth beats are of sinus origin. The intervening QRS complexes are abnormal and are not preceded by a P wave, i.e. they are ventricular in origin. This is the coupled rhythm commonly seen in digitalis intoxication.

Aetiology. Ectopic beats are often found in people with normal hearts. They may be caused by over-indulgence in tea, coffee, tobacco or alcohol, or in association with dyspepsia or anxiety. Ectopic beats may also be found in association with organic heart disease, especially rheumatic carditis, acute myocardial infarction and hypertension. They may be induced by overdosage with digitalis. Atrial and nodal ectopic beats are of no pathological significance although they sometimes precede supraventricular tachycardias. Ventricular ectopic beats are also usually of no importance but in myocardial infarction may be precursors of ventricular tachycardia or fibrillation.

Symptoms. Usually there are no symptoms and the ectopic beats are discovered on routine examination. Sensitive individuals may complain of palpitation or of the heart missing a beat or of a thud from the augmented beat following the ectopic beat. Unwarranted anxiety is often engendered.

Diagnosis. The small premature pulse, the long pause after it or the subsequent augmented beat may be detectable at the wrist. When the ectopic beat occurs too soon for adequate ventricular filling there may be no corresponding pulse beat and ventricular systole can only be detected by auscultation.

Pulsus bigeminus is the name which is applied to the rhythm produced when an ectopic beat and its compensatory pause succeed each normal beat. The heart beats are 'coupled' (Fig. 41). This is seen especially in digitalis overdosage. Sometimes the ectopic beat is too weak to be appreciated at the wrist in which case the pulse rate is halved, but the ectopic beat is heard on auscultation.

Treatment. If ectopic beats are discovered and are not giving rise to symptoms, the patient should not be told of their presence and no treatment is required. When palpitation is complained of but there is no evidence of cardiac disease the patient should be reassured. Excessive consumption of tea, coffee, alcohol or tobacco should be stopped and dyspepsia investigated. A tranquilliser such as diazepam may be given as a temporary measure. Coupled ectopic beats due to digitalis are a warning to reduce the dose of the drug. After acute myocardial infarction, lignocaine by injection may be required (p. 235).

2. Atrial Fibrillation

Atrial fibrillation is a common and important disorder. The precise mechanism is uncertain but is probably due to wavelets of excitation pursuing an erratic course through the atrium depending upon the location of excitable and refractory tissue. Rapid fibrillary waves take the place of normal atrial contractions and the ventricles respond in an apparently random fashion. The atrial rate is about 350 to 600 per minute but the A-V bundle cannot conduct so many impulses and varying degrees of heart block always exist. The ventricular rate is usually about 100 to 150 per minute and the rhythm is totally irregular. The condition may be permanent or paroxysmal. Paroxysmal fibrillation is sometimes the precursor of established fibrillation.

Aetiology

1. Rheumatic heart disease is the commonest cause in the young or middle-aged. It is particularly associated with mitral valve disease and may occur after mitral valvotomy.

2. Ischaemic heart disease is the commonest cause in those past middle age. Temporary atrial fibrillation may follow myocardial infarction.

3. Thyrotoxicosis may be responsible, especially in older patients.

Rarer causes include acute infections, e.g. diphtheria and pneumonia, operations (especially thoracic, e.g. for carcinoma of lung) and pericarditis. It is important to realise that fibrillation may occur in the absence of any other evidence of heart disease (idiopathic fibrillation) and persist for many years. Atrial fibrillation is uncommon in congenital and pulmonary heart disease and in isolated aortic valvular disease.

Effects. Atrial fibrillation may cause or worsen heart failure because of the rapid ventricular rate; the loss of the atrial contribution to ventricular filling may be an additional factor.

The stasis in the atrium favours the formation of thrombus; systemic embolism is an important complication.

Diagnosis. The pulse is completely irregular in time and force but the diagnosis is often more easily made by auscultation, when the gross cardiac irregularity is usually unmistakable. There may be a pulse deficit, e.g. the rate may be 120 at the apex but only 100 at the wrist, due to the fact that some of the weaker beats following a short diastole are not strong enough to open the aortic valve. In cases of mitral stenosis the pre-systolic accentuation, which is dependent on atrial contraction, disappears with the onset of atrial fibrillation.

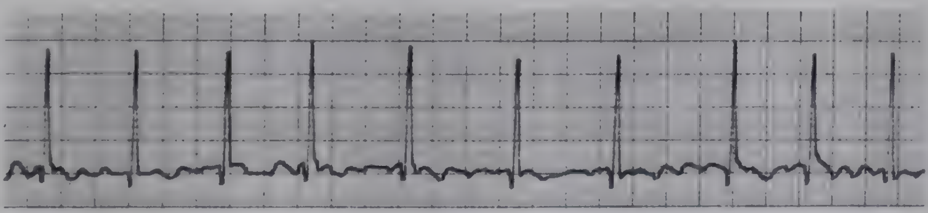


FIG. 42

ATRIAL FIBRILLATION

Ventricular rate approx. 100. Note absence of P waves, continuous rapid, irregular 'f' oscillations and varying intervals between ventricular complexes.

Differential Diagnosis. Exercise usually reduces the irregularity due to ectopic beats. If the pulse rate is above 100, atrial fibrillation is probably the cause of the irregularity. The electrocardiogram of atrial fibrillation is diagnostic, since P waves are absent and usually replaced by irregular fibrillary (f) waves (Fig. 42). In cases of partial heart block with dropped beats and in atrial flutter with varying block, there are usually runs of completely regular beats. An electrocardiogram must be taken for accurate diagnosis.

Prognosis. The prognosis varies with the cause and is best when the underlying disease can be cured, e.g. thyrotoxicosis, or where no cause is found. In mitral stenosis the sudden onset of atrial fibrillation with a rapid ventricular rate often precipitates cardiac failure or leads to systemic or pulmonary embolism. In older subjects, untreated atrial fibrillation is often associated with a normal ventricular rate and there may be little disability.

Treatment. When, as is usually the case, atrial fibrillation occurs as a feature of heart disease, digitalis is used to reduce a rapid ventricular rate. This may result in a striking improvement and is a most valuable effect. In selected cases an attempt may be made to restore sinus rhythm, for example, in patients with fibrillation in whom there is no obvious underlying disease or if fibrillation has apparently been precipitated by an acute infection, myocardial infarction or thoracotomy. This may be achieved by conversion with a direct current defibrillator or with quinidine (p. 233) which slows conduction and increases the refractory period. Sinus rhythm can usually be restored in treated thyrotoxicosis if this has not been achieved by thyroidectomy or antithyroid drugs. In cases of mitral stenosis there is little to be gained from the restoration of normal rhythm, since the arrhythmia is almost certain to return, except when fibrillation has followed valvotomy. Established fibrillation is preferable to paroxysmal attacks. Clot is liable to form in a fibrillating atrium, and with the restoration of normal rhythm there is always the risk of dislodging emboli from the left atrium into the peripheral circulation or from the right atrium into the lungs.

In most cases the object of treatment is to control the ventricular rate and this can usually be done satisfactorily with digitalis (p. 248). If necessary propranolol or practolol (p. 235) is a useful adjuvant. In cases of recent onset, anti-coagulation should be undertaken because of the high risk of embolism.

3. Atrial Flutter

There is rapid, regular atrial action at a rate of 250 to 350 per minute and the ventricles usually respond to every other beat (i.e. 2:1 heart block). Sometimes the response is slower, e.g. 3:1 or 4:1 block, and occasionally the degree of heart block varies so that the rhythm is irregular.

Aetiology. The aetiology of atrial flutter is essentially the same as atrial fibrillation but the condition is far less common.

Effects. Cardiac failure is often precipitated; thrombo-embolism is less common than in atrial fibrillation.

Diagnosis. When the patient has constant regular tachycardia of 130-160 beats per minute which is uninfluenced by changes of posture or mild exercise, atrial flutter may be the cause. Occasionally the atrial waves may be seen in the jugular veins, but most often an electrocardiogram is needed to confirm the diagnosis (Fig. 43). Flutter waves have a regular saw-like appearance and are interrupted by the ventricular complexes. Sometimes the ventricular rate may suddenly double or halve. Vagal stimulation, e.g. pressure over the carotid sinus in the neck, may halve the rate temporarily but sinus rhythm is not restored. In paroxysmal supraventricular tachycardia, by contrast, vagal stimulation will either terminate the paroxysm or have no effect. With varying A-V block the radial pulse may be indistinguishable from that in atrial fibrillation.

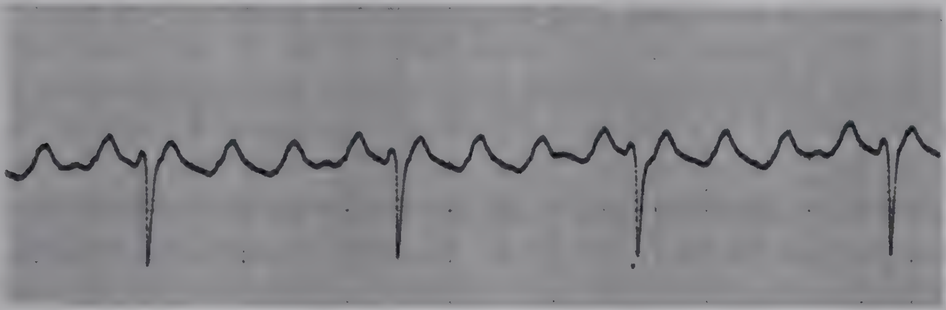


FIG. 43

ATRIAL FLUTTER

'Saw-tooth' atrial complexes at rate of 250 per minute.
There is 4:1 AV ratio.

Treatment. Digitalis should be given in full dosage and this may produce atrial fibrillation or sinus rhythm. Sinus rhythm is usually restored within a few days. If not, treatment with quinidine or electrical conversion as for atrial fibrillation may be tried.

4. Paroxysmal Tachycardia

Paroxysmal tachycardia is characterised by attacks of rapid heart action due to a regular succession of ectopic beats lasting from a few seconds to several days. The electrocardiogram of an attack distinguishes the following types.

SUPRAVENTRICULAR TACHYCARDIA

(*a*) Atrial; originating somewhere in the atria other than in the S-A node. Paroxysmal atrial tachycardia is by far the most common type and usually occurs in young people without organic heart disease. The cause is unknown. The onset of the paroxysms may be influenced by nervousness but usually occurs for no obvious reason. Occasionally tobacco, alcohol, coffee, overeating or gastric distension is responsible.

(*b*) Atrial tachycardia with A-V block. This may be a sign of digitalis toxicity, especially if hypokalaemia is present.

(*c*) Junctional (nodal): originating in the pacemaker tissue adjacent to the A-V node.

VENTRICULAR TACHYCARDIA

Paroxysmal ventricular tachycardia is much less common and more serious than atrial tachycardia. It is usually seen in people with ischaemic heart disease.

It may be an immediate sequel of coronary occlusion and precede ventricular fibrillation. It is sometimes caused by over-dosage with digitalis.

Clinical Features. If the paroxysm is brief, symptoms may be absent. Usually there is a sudden sensation of fluttering in the chest, often described as palpitation. Sometimes the attack is very distressing. The heart rate is about 180 per minute (150 to 250) and quite regular. The rate is uninfluenced by rest, posture or exercise. If the paroxysm lasts more than about 15 minutes, many patients are surprised to find they pass large quantities of urine. This occurs frequently enough to be helpful in diagnosis. Rarely with a diseased heart, or in old age, paroxysmal tachycardia may lead to heart failure. Supraventricular tachycardia may be terminated abruptly by carotid sinus massage as described on page 233. The electrocardiogram shows a series of rapidly occurring ectopic beats of supraventricular or ventricular type (Figs 44 and 45). The cessation often appears to the patient to be less abrupt than the onset due to a period of sinus tachycardia following the paroxysm.

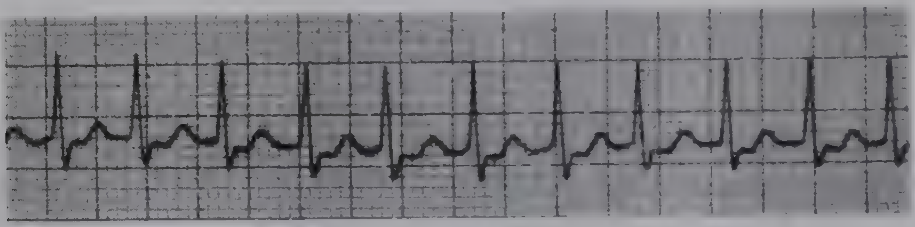


FIG. 44

PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA

Rate approximately 180. P waves not visible.

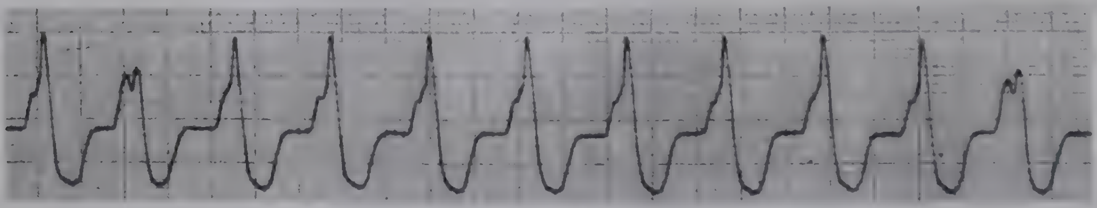


FIG. 45

PAROXYSMAL VENTRICULAR TACHYCARDIA

Rate approximately 140. Note large, slurred complexes each resembling a ventricular premature beat.

Differential Diagnosis

SINUS TACHYCARDIA. The rate in sinus tachycardia is rarely so fast and is influenced by emotion, exercise and posture. The onset and cessation are gradual. Palpitation caused by panic is often wrongly diagnosed as paroxysmal tachycardia.

ATRIAL FLUTTER. The ventricular rate in atrial flutter rarely exceeds 160, and although, as with paroxysmal tachycardia, the rate is uninfluenced by exercise and posture, it may be suddenly halved by doubling of the A-V block.

Prognosis. The majority of paroxysms of supraventricular tachycardia give rise to few symptoms and cease spontaneously but they can be unpleasant. Paroxysmal atrial tachycardia most often occurs with a heart that is otherwise normal and the prognosis is good. When attacks are frequent or disabling it is usually possible to improve the situation with treatment. Ventricular tachycardia seldom occurs in a heart which is otherwise normal and may be life threatening as a complication of myocardial infarction.

Treatment. No treatment is needed if the attack is of short duration. In other cases simple sedation may be sufficient.

ATRIAL. Increase in vagal tone may arrest the paroxysm and this is most effectively achieved by carotid sinus massage. The sinus is situated close to the bifurcation of the common carotid artery opposite the angle of the jaw. The thumb should be placed over the position of maximum pulsation and firm massage applied to the vessel and against the spine for not longer than 10 seconds, first on one side and, if necessary, then on the other, but never on both together. Mere pressure is rarely sufficient. The heart should be auscultated with the chest-piece of the stethoscope held over the apex beat. If possible, the procedure should be monitored by a continuous ECG record. Simpler methods are sometimes effective, such as holding the breath for as long as possible or by performing the Valsalva (forcible expiration with glottis closed) or Muller (deep inspiration with glottis closed) manoeuvre. Retching or vomiting may terminate the attack and this may be induced by putting a finger down the throat.

Practolol (p. 235) is now the drug of choice. Digitalis is also an effective drug for arresting an attack and can be given in the form of digoxin, 1 mg intravenously, or an initial dose of 1 mg may be given orally followed by 0·25 mg four-hourly until the attack is arrested or until nausea results. Direct current conversion may be necessary if other methods fail.

VENTRICULAR. Measures which increase vagal tone are ineffective. Lignocaine 50-100 mg intravenously will terminate most attacks. If this fails procainamide at the rate of 100 mg a minute up to a maximum of 2·0 g by intravenous injection is often effective. The injection should be given slowly and stopped immediately if there is a significant fall in the blood pressure. Digitalis should not be given if it is likely to have caused the arrhythmia. Direct current conversion is a simple and safe form of treatment if the apparatus is available.

Prevention of Further Attacks. Exciting causes should be avoided wherever possible. Digitalis or practolol are both useful in reducing the frequency of attacks of supraventricular tachycardia. Ventricular tachycardia may be prevented by lignocaine, procainamide or quinidine.

Anti-arrhythmic Drugs

QUINIDINE AND PROCAINAMIDE

If facilities for electrical conversion are not available quinidine and procainamide are useful drugs for restoring normal rhythm in selected cases of cardiac arrhythmia and for the prevention of recurrent attacks. Administration is not without risk but this is slight in experienced hands when the patient is under close observation, with facilities for electrocardiographic control. For this reason treatment should rarely be initiated in general practice.

Actions. These drugs prolong the refractory period of the myocardium and slow the rate of spontaneous depolarisation. They also depress conduction.

Indications

ATRIAL FIBRILLATION. Restoration of sinus rhythm is rarely indicated if fibrillation has been present for more than a few months or if cardiac failure, gross enlargement of the heart or other evidence of severe underlying disease is present. Quinidine is most likely to be effective in cases of recent origin.

ATRIAL FLUTTER. Quinidine may be used to try and restore normal rhythm where digitalis, the drug of choice, has not been effective.

PAROXYSMAL TACHYCARDIA. Quinidine and procainamide should be used for the treatment of paroxysmal supraventricular tachycardia if other measures fail and are often effective in the treatment and prevention of attacks of paroxysmal ventricular tachycardia or ventricular fibrillation.

PROPHYLAXIS. Quinidine or procainamide is useful for the prevention of recurrent attacks of most forms of paroxysmal cardiac arrhythmia, but other drugs such as propranolol may be found effective. Quinidine or procainamide may be useful for preventing ectopic beats in the occasional instances where they give rise to unpleasant symptoms which cannot otherwise be controlled.

Administration. Quinidine and procainamide are normally given by mouth, but for urgent cases a preparation of procainamide suitable for intravenous injection is available.

Very occasionally idiosyncrasy to quinidine is present. If no toxic effects (see below) develop after the first dose, treatment should be continued. Since many patients revert to sinus rhythm on a small dose it is best to begin with 0·2 g t.d.s. and gradually increase the daily dose until the desired effect is obtained. Should normal rhythm be restored a maintenance dose of 0·2-0·4 g t.d.s. should be given until normal activities have been resumed. Toxic symptoms which are common include headache, tinnitus, blurring of vision, nausea, vomiting, diarrhoea and occasionally mental disturbances. Purpura may occur. Rarely, sudden death has been reported from cardiac standstill or ventricular fibrillation. Warning signs may be disclosed by serial electrocardiograms, notably widening of the QRS interval.

Procainamide has similar properties to quinidine and in particular it depresses the irritability of ventricular muscle. It may be used for the treatment of ventricular tachycardia but must be given with caution because hypotension may result. Hypotension should be promptly treated by raising the foot of the couch or bed. In emergency procainamide may be given intravenously at a rate of 100 mg/min up to a total of 1 g. The blood pressure and electrocardiogram should be recorded between each increment. The prophylactic dose is 0·5 g orally four hourly.

If given for several weeks procainamide may produce neutropenia or a syndrome like systemic lupus erythematosus (p. 780).

Lignocaine

Lignocaine has a similar action to quinidine and procainamide but does not depress the myocardium or result in hypotension. It is the drug of choice for the control of ventricular ectopic beats and of ventricular tachycardia after acute myocardial infarction (p. 270). The initial dose is 50-100 mg given intravenously and followed if necessary by 500 mg in 500 ml dextrose as a slow infusion in 6-8 hours. This should be continued for 1-2 days. If anti-arrhythmic therapy is still required after this time, an orally administered drug such as procainamide or practolol should be used.

Propranolol, Practolol and Oxprenolol

These drugs block the adrenergic beta receptors and thus counteract the stimulating action of sympathomimetic amines on the rate and force of myocardial contraction. They are often effective in reducing the ventricular rate or restoring sinus rhythm in attacks of paroxysmal tachycardia, especially if induced by digitalis. By producing bradycardia and limiting cardiac acceleration with exercise, myocardial ischaemia may be reduced in patients with coronary disease. They are therefore frequently useful in the treatment of intractable angina. Propranolol may exacerbate bronchial asthma; practolol is less likely to do so and is to be preferred in treating arrhythmias. It can be given in a dose of 5-20 mg slowly intravenously; the oral dose is 100-200 mg twice daily. Oral propranolol and oxprenolol are perhaps more effective in the treatment of angina. The dosage used for this purpose is 40-120 mg four times daily. They should be given cautiously to patients at risk of developing cardiac failure.

Phenytoin

This anti-convulsant drug has been used with some success in the treatment of ventricular and supraventricular arrhythmias, especially if induced by digitalis. It can be given either as a slow intravenous injection at a rate of 50 mg/min up to a total of 300 mg, or orally in a dose of 200 mg every four to six hours. As with other cardiac depressants, hypotension may be induced by excessive administration.

Heart Block

Heart block may be slight and reflected only in prolongation of the P-R interval in the electrocardiogram; or moderate so that impaired conduction of the impulse from the atria results in some 'dropped' ventricular beats; or so great that the ventricles adopt an independent rhythm.

Sino-Atrial (S-A) Block

A complete cardiac cycle is missed so that a gap appears in the pulse. This condition is uncommon and of little clinical importance, being due to increased vagal tone. The electrocardiogram shows that both atrial and ventricular complexes are absent (Fig. 46).

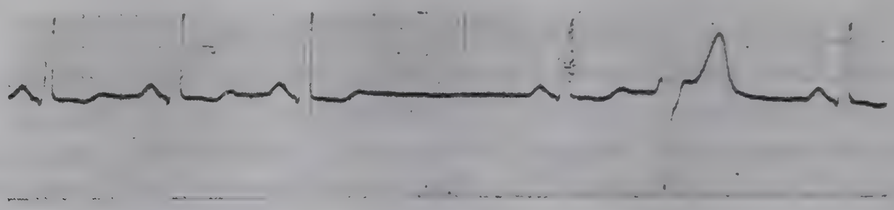


Fig. 46

Sino-Atrial Block

Rate 68. Note pause due to absence of entire PQRST. A ventricular extrasystole follows the fourth complex.

Atrio-ventricular (A-V) Block

Conduction between the atria and ventricles is impaired.

(1) Delayed A-V Conduction (first degree block)

P-R interval is prolonged beyond the upper limit of normal (0·2 sec.) (Fig. 47).

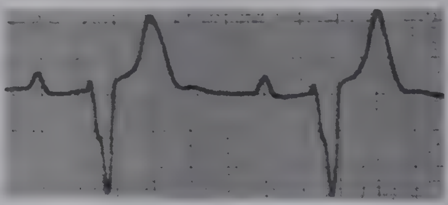


Fig. 47

Delayed A-V Conduction

Rate 50. P-R interval 0·36 of a second.

(2) Partial Heart Block (second degree block)

Some impulses from the atria fail to get through to the ventricles, i.e. dropped beats occur. Sometimes there is progressive lengthening of successive P-R intervals followed by a dropped beat (Wenckebach's phenomenon, Fig. 48).

(3) Complete Heart Block

No impulses from the atria reach the ventricles, which beat at their intrinsic rate of about 40 beats per minute (Fig. 49).

Aetiology. Depression of conductivity is most commonly due to ischaemia, fibrosis or inflammation of the bundle of His, or to vagal stimulation.

1. *Coronary Artery Disease.* This is the chief cause of acute heart block.

2. *Focal Fibrosis.* Idiopathic focal fibrosis, strategically situated, is a common cause of chronic heart block, particularly in the elderly.

3. *Rheumatic Fever.* Prolongation of the P-R interval is common but more severe grades are rare.

4. *Digitalis.* This drug more frequently causes the milder degrees of impaired conduction. The action is therapeutic when it is used to reduce the rapid ventricular rate accompanying atrial fibrillation and flutter. Complete heart block may be a late manifestation of digitalis poisoning.

5. *Aortic Stenosis.* This may result in functional coronary insufficiency or calcification may extend into the interventricular septum and interfere with the conducting tissues.

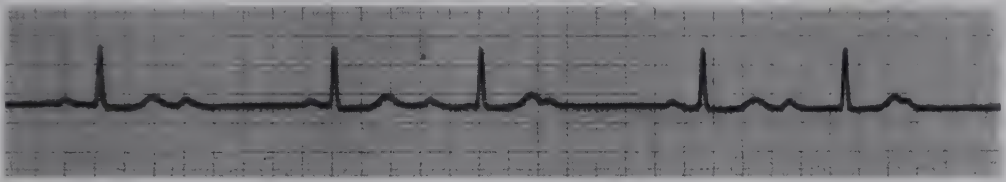


FIG. 48

PARTIAL HEART BLOCK (WENCKEBACH'S PHENOMENON)

Rate 88. Progressive lengthening of successive P-R intervals followed by dropped ventricular beat.

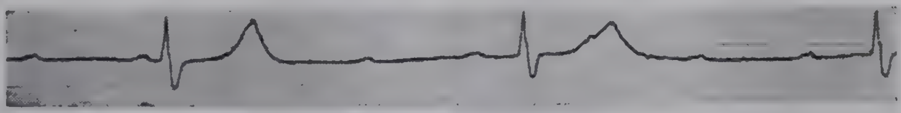


FIG. 49

COMPLETE HEART BLOCK

Atrial rate 100. Ventricular rate 34. Note complete dissociation of atrial and ventricular complexes.

6. *Congenital Heart Disease.* Complete heart block occasionally results from a congenital maldevelopment of the bundle. The condition is benign and the degree of bradycardia often less marked than in other forms (e.g. 50 to 60 per minute).

7. *Disorders of Atrial Rhythm.* Extreme supraventricular tachycardia, e.g. from atrial fibrillation, atrial flutter or paroxysmal tachycardia, may lead to fatigue and refractoriness of the A-V node and bundle.

8. *Cardiomyopathies and Myocarditis*, e.g. diphtheria. These are rare causes of conduction defects.

Clinical Features. DELAYED A-V CONDUCTION. This cannot be diagnosed clinically but only on the electrocardiogram. Its recognition is sometimes of help as an indication of active rheumatic carditis.

PARTIAL HEART BLOCK. When the atrial and ventricular contractions bear a simple ratio to one another such as in 2 : 1 and 3 : 1 block, the pulse is slow and regular. Change in the degree of partial heart block may give rise to sudden changes in pulse rate. The degree of block may be diagnosed by comparing the number of atrial contractions ('a' waves in the jugular pulse) with the carotid pulse. More complex ratios between atrial and ventricular contractions such as 3:2 or 4:3 block give rise to 'dropped beats'. On auscultation it can be appreciated that there has been no ventricular beat, thus distinguishing the condition from ectopic beats. The first heart sound may vary in intensity. The Wenckebach phenomenon (p. 237) is due to progressive fatigue of the A-V bundle with recovery following the rest period when the dropped beat occurs (Fig. 48). Partial heart block is usually transient and may occur during an acute infection, from digitalis overdose, or from coronary heart disease.

COMPLETE HEART BLOCK should be suspected when the pulse rate is slow (30 to 40) and regular, and does not vary with exercise. There is complete dissociation between the jugular 'a' waves and the carotid pulses. There may be varying intensity of the first heart sound and audible atrial sounds. Venous 'cannon' waves in the neck may be seen when the right atrium contracts against a closed tricuspid valve.

ADAMS-STOKES SYNDROME. When cerebral blood flow ceases as a result of ventricular asystole, tachycardia or fibrillation, syncope occurs rapidly. Convulsions will occur if the heart does not begin to beat again within about 10 seconds, and death will result if asystole is prolonged from 2 to 3 minutes. The skin blanches and later cyanosis occurs. When the heart starts beating again there is a characteristic flush as the emptied vessels are filled with blood. The syndrome is a complication of complete heart block or less commonly partial heart block. Patients who have repeated attacks may be aware of the imminence of unconsciousness, but frequently syncope occurs without warning. Breathing may continue after the heart has stopped.

Treatment. Adams-Stokes attacks are usually self-limiting but, if not, may be terminated by a blow on the precordium, closed-chest massage or electrical pacing of the heart.

Complete heart block in acute myocardial infarction requires treatment to prevent undue bradycardia or asystole. Isoprenaline, as an intravenous infusion (1-5 mg in 500 ml dextrose) is effective in increasing the ventricular rate. Electrical pacing may be carried out by advancing a special electrode from a peripheral vein until its tip lies against the endocardium of the right ventricle. Its proximal end is attached externally to a pulse generator. Pacing is usually required for only a few days.

Treatment by drugs or pacing is also required when chronic heart block is responsible for heart failure or Adams-Stokes attacks. Long-acting isoprenaline may be given in a dose of 30 mg or more four times daily. Alternatively, a pulse generator may be permanently placed beneath the skin and electrical pacing instituted.

Prognosis. The outlook may be serious but depends on the cause. In myocardial infarction, the block is usually transient. In chronic heart block the prognosis is often good with effective pacemaking.

Bundle Branch Block

This term is applied to a block in conduction in either the right or left branch of the A-V bundle. Most cases are due to coronary artery disease. Rheumatic heart disease and congenital heart disease are occasional causes. Sometimes there is no evidence of underlying disease.

The diagnosis can only be made by means of an electrocardiogram. The QRS interval is increased to 0·12 sec. Examples of right and left bundle branch block are shown in Figures 31 and 32. The clinical manifestations, treatment and prognosis are those of the underlying disease.

Cardiac Arrest

Cardiac arrest signifies sudden cessation of an effective circulation. It will often respond to appropriate treatment if this is given within approximately five minutes, after which irreversible cerebral damage occurs. The development of the technique of closed-chest cardiac massage (external cardiac massage) together with mouth-to-mouth artificial respiration has greatly improved the prognosis (Fig. 50). Doctors, nurses, ambulance drivers and attendants should all receive instruction in this vitally important form of first aid.

Cardiac arrest is due to ventricular asystole or ventricular fibrillation; these two conditions can be distinguished only by electrocardiography or by direct inspection of the heart.

It occurs most frequently after myocardial infarction but also during general anaesthesia, in the course of surgical operations especially thoracotomy, and even during minor diagnostic procedures such as intravenous pyelography. It may also be due to hypersensitivity to a drug such as penicillin. Electrocution is another cause of cardiac arrest.

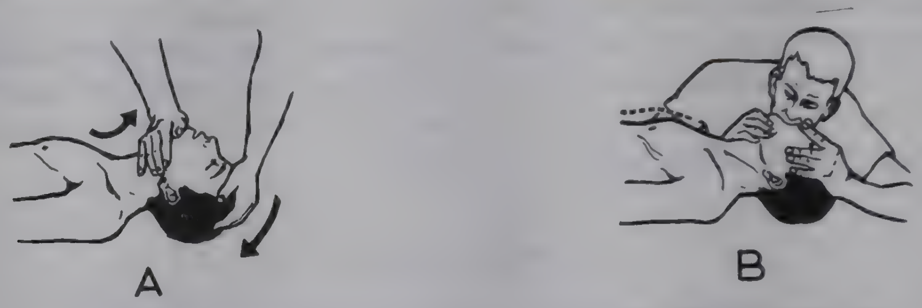
The diagnosis is based on sudden loss of consciousness and the absence of the pulse in the carotid or femoral artery, confirmed if possible by an electrocardiogram. Treatment often has to precede ECG confirmation.

Treatment. The immediate objective is to restore an oxygenated blood supply to the brain and to the heart muscle, and for this purpose the following actions should be taken.

A smart blow should be given to the chest with the hand or fist and both legs elevated to 90 degrees for 15 seconds. If the heart does not start beating immediately, as indicated by the return of the carotid or femoral pulse, cardiopulmonary resuscitation must be started.

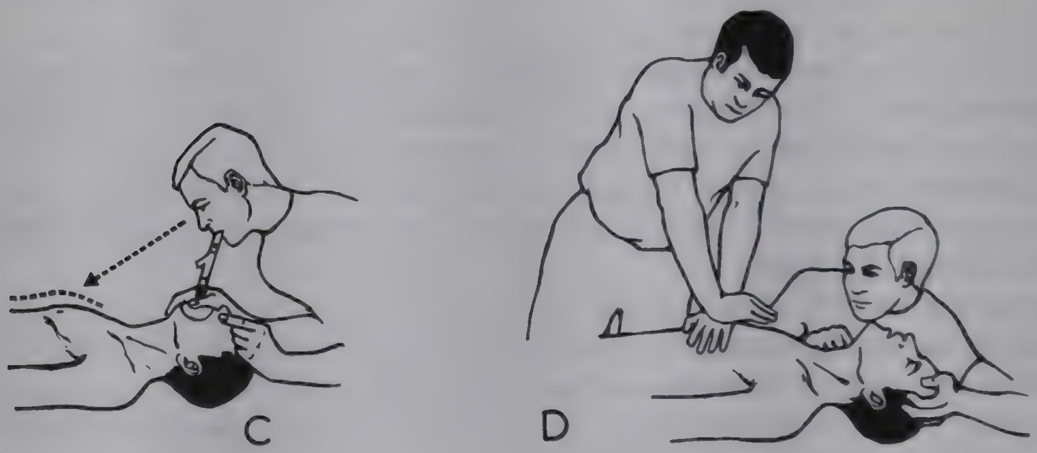
Technique of Cardiopulmonary Resuscitation. The object of closed-chest cardiac massage is to empty the blood from the ventricles by compressing the heart between the sternum and the spinal column (Fig. 50). This is accomplished by laying the patient on his back on a hard surface, such as the floor, or inserting a board behind his thorax. The operator places his hands, one on top of the other, on the lower end of the patient's sternum immediately above the xiphisternum and commences forcible rhythmic compressions at the rate of 60 to 80 per minute. The force of the compression must be sufficiently great to produce pulsation in the carotid and femoral arteries.

When cardiac arrest occurs, respiration usually stops or respiration may have ceased prior to cardiac arrest. The head should be hyperextended and the chin raised to clear the airway. Mouth-to-mouth breathing is then commenced; this can be done directly (Fig. 50B) or through a specially designed tube if this is available (Fig. 50C).



A. Head hyperextended and chin raised

B. Direct mouth-to-mouth breathing



C. Indirect mouth-to-mouth breathing

D. Cardiac massage

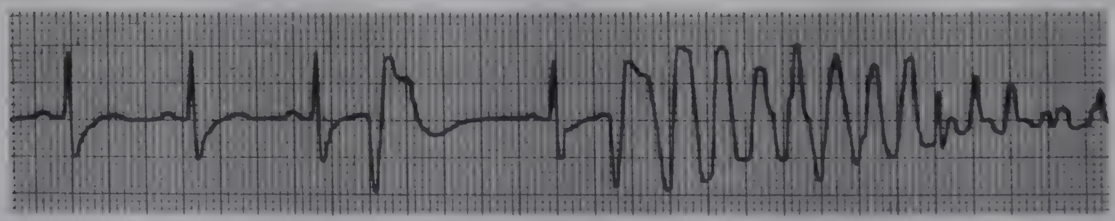


FIG. 50

EMERGENCY RESUSCITATION

The ECG shows the development of ventricular fibrillation from sinus rhythm. This is the commonest cause of cardiac arrest.

Cardiac massage (Fig. 50D) and artificial respiration must be continued so long as there seems any chance of the heart beating again. This may occur spontaneously if the cause of the cardiac arrest is ventricular asystole, but it is unlikely if the arrest is due to ventricular fibrillation. If ventricular fibrillation is present it must be corrected by means of an electric defibrillating machine which is effective when applied externally to the chest wall. As a result ventricular fibrillation is changed to ventricular asystole; in most cases the heart starts beating again either spontaneously or after a short period of continued closed-chest cardiac massage. If cardiac contractions are restored but the blood pressure remains low an isoprenaline intravenous infusion (2 mg in 500 ml of 5 per cent dextrose) should be given and repeated as required. If electrical defibrillation fails it may be successful after an intravenous injection of lignocaine (50-100 mg). If asystole is present, the heart can be stimulated by an electrical pacemaker. The acidosis which immediately follows even temporary arrest must be corrected by the intravenous administration of 150 mEq of bicarbonate in the first 10 minutes and repeated as long as the circulation remains inadequate. Persistence of fixed dilatation of the pupils indicates that cerebral damage is irreversible.

Differential Diagnosis. Loss of consciousness is most frequently due to syncope from a vaso-vagal attack; much less commonly it may be due to cardiac standstill or other causes of cardiac syncope (p. 242).

Other causes of sudden death include rupture of the heart following myocardial infarction, rupture of the aorta from dissecting aneurysm (p. 303) and massive pulmonary embolism (p. 282).

Syncope

By syncope is meant transient loss of consciousness which is usually due to decreased cerebral blood flow. Contrary to popular belief, syncope is rarely due to heart disease. More often it is caused by reflex peripheral vasodilatation which leads to a pooling of blood, with a consequent reduction in cardiac output and cerebral blood flow as in the vasovagal or fainting attack.

Vasovagal attacks are usually due to emotional stimuli such as fear, disgust or surprise, e.g. at the sight of blood or witnessing an accident. Occasionally syncope may be due to pain. Lack of food, hot stuffy atmospheres and prolonged standing are common predisposing factors.

The attack comes on rapidly and usually unexpectedly, although the cause may be apparent. Weakness, light-headedness, nausea and a sinking feeling in the epigastrium are followed by a period of unconsciousness which usually lasts for a few seconds or minutes, but may be longer. The subject is pale and clammy, the blood pressure low and the pulse rate usually slow but sometimes rapid. Recovery follows because fainting often removes the precipitating factor and the inevitable assumption of the recumbent posture facilitates the venous return to the heart and hence cerebral flow.

Postural hypotension is a cause of syncope which may occur on standing up suddenly or standing still on the parade ground. It is especially liable to occur in elderly patients who are recovering from acute illness. The administration of sympathetic blocking drugs may also be responsible.

Hypersensitive carotid sinuses may cause loss of consciousness following pressure on the sinus as occurs with abrupt movements of the neck.

The strain of coughing or micturition occasionally causes syncope; in each case the patient is performing a Valsalva manoeuvre which raises the intrathoracic pressure and obstructs venous return.

Cardiac syncope may be due to cardiac standstill as occurs in Adams-Stokes attacks from heart block (p. 238), to massive pulmonary embolism, to extreme degrees of tachycardia or to temporary ventricular standstill at the onset or end of a paroxysm of tachycardia. It may occur in severe aortic or mitral stenosis when the cardiac output cannot increase with exertion and there is vasodilatation in the muscles.

CARDIAC FAILURE

Cardiac failure exists when the output of the heart is insufficient for the needs of the tissues. It may be acute or chronic. The picture of acute failure may be one of 'shock' with severe hypotension (p. 251) but the chief clinical features of cardiac failure, whether acute or chronic, are associated with fluid retention: this may affect predominantly the lungs (left heart failure) or the systemic veins and liver and produce peripheral oedema (right heart failure). Left and right heart failure frequently co-exist.

Pathophysiology

Over a given period of time the output of the heart depends upon the stroke volume and the heart rate. The stroke volume is determined by a number of factors of which the most important are:

(1) *The Volume of the Ventricle at the Onset of Ventricular Systole* (*the End-diastolic Volume*). In accordance with Starling's Law, the force of contraction of a muscle fibre is a function of its length at the onset of contraction. This is true both of the individual unit of contraction—the sarcomere—as well as of the ventricular myocardium as a whole. Because the normal heart operates at a length well below the point of maximum tension, the larger the end-diastolic volume, the more forceful will be the subsequent systole. Eventually, however, the ventricle may be stretched beyond the physiological range and there will then be a fall-off in contraction.

As end-diastolic volume increases, so does end-diastolic pressure. Within the physiological range of end-diastolic volumes, the pressure rises comparatively slightly, but when the left ventricle becomes markedly distended, there may be a considerable rise in end-diastolic pressure with a consequent rise in the pressures of the left atrium and pulmonary vessels.

In the normal heart, the venous return is a major factor in determining the end-diastolic volume. In certain diseases in which there is a raised cardiac output such as thyrotoxicosis and severe anaemia, the venous return is markedly augmented and an abnormal degree of filling occurs leading to dilatation of the heart. Dilatation also occurs when there is an increased volume load on the heart due to reflux of blood through valves such as occurs in mitral regurgitation; in this condition the left ventricle has to accommodate in diastole not only the blood that must be propelled into the aorta but also the substantial volume which is regurgitated into the left atrium during systole. Up to a point, dilatation is an effective way of increasing the output of the heart in accordance with Starling's Law, but increased tension is developed in the myocardium and leads to an increased oxygen demand and eventually to hypertrophy of the myocardium.

(2) *The Pressure Load against which the Ventricle has to Contract.* Normally this is largely determined by the resistance of the small arteries. Obstruction to the outflow of the left ventricle (aortic stenosis) and the increased blood pressure of systemic hypertension both increase the pressure load. The left ventricle responds to this by contracting more forcefully; eventually it hypertrophies. Up to a point, hypertrophy is physiological but when it becomes extreme, the thickening of the muscle outstrips its blood supply and the muscle may become ischaemic and fibrotic.

(3) *Contractility of Myocardium.* When the other factors are held constant, stroke volume depends upon the contractility of the myocardium. In health, this is largely dependent upon cardiac sympathetic nervous activity, but is also influenced by circulating catecholamines. Drugs which increase myocardial contractility (inotropic drugs) include isoprenaline and the cardiac glycosides. Quinidine, procainamide and beta adrenergic blocking drugs such as propranolol are negatively inotropic.

(4) *Other Factors.* The contractility of the diseased heart may also be impaired by hypoxia and by damage to the muscle cells as occurs in ischaemic heart disease, cardiomyopathy and rheumatic heart disease. An additional factor in ischaemic heart disease is the development of myocardial infarction, which is responsible for necrosis and scarring of areas of heart muscle which become non-contractile.

Compensatory Mechanisms in Cardiac Failure

Although in most cases of cardiac failure the primary disturbance lies in the heart itself, many of its manifestations are the consequence of compensatory mechanisms of which the most important is the retention of salt and water.

In cardiac failure, an increase in total body sodium and water is virtually invariable. Extracellular fluid and plasma volume increase but the intracellular fluid remains essentially unchanged. The sodium retention results both from the decrease in the amount of sodium filtered by glomeruli and an increase in sodium reabsorption by the tubules. There is a disproportionate decrease in renal blood flow and a reduction in sodium filtration, but this mechanism is inadequate to account for sodium retention that occurs; the mechanism of the increased tubular reabsorption of sodium is as yet uncertain.

One important feature of cardiac failure is the rise in venous pressure which affects the pulmonary veins when the left side of the heart is diseased, and the systemic veins in right-sided heart failure. The rise in venous pressure is to some extent the consequence of the increased blood volume secondary to sodium and water retention. However local factors within the heart are also important and determine which veins become congested. Thus, with mitral stenosis, there is a rise in left atrial pressure which is transmitted to the pulmonary veins. In right-sided cardiac failure as occurs in lung disease the pressures in the pulmonary arteries, the right ventricle and the right atrium rise and lead to systemic venous congestion.

Causes of Heart Failure

The heart may fail as a whole as in thyrotoxicosis or myocarditis, but in the early stages, and sometimes throughout the whole course, failure of the left or of the right side of the heart may be recognised as an isolated clinical condition. Left ventricular failure is usually due to hypertension, coronary atherosclerosis or aortic valvular disease. Left-sided failure may also be said to occur when the left atrium cannot empty satisfactorily, as occurs in mitral stenosis. Right-sided failure is often secondary to preceding left-sided failure. It may, however, result from certain diseases of the lungs, notably emphysema, from congenital heart disease, e.g. pulmonary stenosis or septal defects or from conditions which impede the flow of blood into the right side of the heart, e.g. tricuspid stenosis or some cases of constrictive pericarditis.

Left-sided Cardiac Failure

Although pulmonary congestion is the cardinal feature of all forms of left-sided failure, the clinical course of failure of the left ventricle is not the same as when failure is secondary to mitral stenosis.

Left ventricular failure from coronary occlusion may be of acute onset but when the underlying disease is of long standing, as is usually the case in hypertension or aortic valvular disease, the powerful left ventricle has time to compensate by gradual hypertrophy. In such cases dyspnoea is not usually evident for many years. When failure does occur it tends to be steadily progressive and life is rarely prolonged for more than one to three years.

When a mitral valve defect is the predominant factor and the myocardium is relatively little affected, dyspnoea is usually present for many years. The long-standing increase in pressure in the pulmonary circulation gradually leads to right-sided failure with venous congestion and oedema. This often responds to treatment but it is common for episodes of cardiac failure to recur at ever-decreasing intervals and with ever-increasing severity. With severe mitral stenosis attacks of pulmonary oedema may be precipitated by exercise, pregnancy or tachycardia from any cause, such as emotion or atrial fibrillation.

Clinical Features. The principal manifestations of left ventricular failure are dyspnoea, cough, crepitations at the bases of the lungs, enlargement of the heart due to hypertrophy and dilatation of the left ventricle, triple rhythm and pulsus alternans.

DYSPNOEA. This is due to pulmonary venous congestion from failure of the left side of the heart. This reduces lung compliance, increases the work of breathing and results in rapid shallow respiration. The vital capacity is correspondingly reduced. Subsequent right-sided failure may partially and temporarily relieve the dyspnoea by reducing the amount of blood pumped into the lungs. In such circumstances the patient may be agreeably but mistakenly encouraged by his apparent progress.

Dyspnoea on Exertion. This must be assessed in relation to the patient's age, weight and physical fitness. The first evidence is usually undue breathlessness on hills, or the necessity to pause for breath after one or two flights of stairs. The housewife finds the heavier household tasks such as scrubbing and polishing too difficult. Eventually there is dyspnoea when walking on level ground which at first makes conversation impossible and then imposes a slower pace.

Dyspnoea at Rest. Later dyspnoea will be present at rest and finally the patient cannot lie flat without distress (orthopnoea).

Paroxysmal Dyspnoea. Attacks usually occur at night, often wakening the patient who sits up or even gets out of bed and walks to an open window gasping or choking. There is often a dry repetitive cough, but with the most severe and prolonged attacks there may be watery, frothy sputum which is often blood-stained (pulmonary oedema). The patient is anxious, pale, sweaty and cyanosed. The pulse is rapid and the blood pressure often raised. In some cases wheezing accompanies the dyspnoea (cardiac asthma) and then the differentiation from bronchial asthma may be difficult. A long history of similar attacks, a personal or family history of allergic disorders, extreme expiratory difficulty, the tendency to occur in young people and the absence of signs of heart disease are features of bronchial asthma.

Cheyne-Stokes Respiration. This is a periodic form of breathing characterised by alternate phases of waxing and waning. It is particularly liable to occur in elderly patients with left ventricular failure and decreased cerebral blood flow; it is also seen in uraemia and patients with intracranial disease, e.g. tumour or vascular accidents. It is a sign of serious prognostic importance. It is aggravated by anything which further depresses the respiratory centre, e.g. sleep and the administration of sedative drugs. The principal factor in its production is depression of the medullary centres from decreased blood flow. Oxygen lack, accentuated during apnoea, sensitises the centre to the stimulus of carbon dioxide. The force and depth of respiration then increase and the resulting reduction of carbon dioxide in the blood leads to apnoea, carbon dioxide accumulates and the cycle begins again. Each phase lasts from about ½ to 1 minute. In cardiac cases with pulmonary congestion the hyperpnoeic phase may be very distressing and waken the patient from sleep.

COUGH. Cough may result from pulmonary congestion or oedema or from superimposed infection. It is frequently troublesome at night and may be responsible for insomnia. Pulmonary congestion from cardiac failure may mimic chronic bronchitis in elderly persons.

PULSUS ALTERNANS. (p. 208). This is indicative of a poor prognosis.

ENLARGEMENT OF THE HEART. Enlargement of the heart from left ventricular hypertrophy is always present when failure is due to hypertension or aortic valvular disease and the heaving impulse can be felt at the apex. Less obvious enlargement is frequently present in long-standing coronary disease.

TRIPLE RHYTHM. An extra, atrial (fourth) heart sound may be heard in late diastole in left ventricular failure or hypertrophy. It is usually maximal at the apex and is sometimes palpable as well as audible. An extra (third) sound in early diastole is a sign of rapid ventricular filling from an increased left atrial pressure. 'Gallop rhythm' (p. 212) may be audible.

CREPITATIONS AT THE BASES OF THE LUNGS which persist after coughing are the most important sign of pulmonary oedema. Rhonchi may also be present.

HYDROTHORAX may occur on one or both sides. No pain is associated with the development of this transudate.

RADIOLOGICAL EXAMINATION may reveal enlargement of the heart and its individual chambers and signs of congestion or oedema of the lungs (p. 223).

ELECTROCARDIOGRAPHY may show evidence of left ventricular hypertrophy or of ischaemic heart disease.

Right-sided Cardiac Failure

Right-sided failure is usually secondary to left-sided failure and is therefore often associated with pulmonary congestion and dyspnoea. Increasing pressure in the lesser circulation is followed by dilatation and hypertrophy of the right ventricle. Sometimes the heart will fail as a whole and in such cases the clinical manifestations are principally those of right-sided failure. Isolated right-sided failure may occur as a result of pulmonary disease, e.g. chronic bronchitis, emphysema, and in certain forms of congenital heart disease, e.g. pulmonary stenosis. When the right ventricle begins to fail, systemic venous congestion and oedema occur.

Clinical Features

RAISED JUGULAR VENOUS PRESSURE. The importance of distension of the neck veins as evidence of increased venous pressure from cardiac failure is discussed on page 209. An expansile wave in systole is frequently present from functional tricuspid regurgitation.

OEDEMA. The principal factors in the pathogenesis of cardiac oedema are:

1. Retention of water in the body due to increased reabsorption of sodium from the tubules.
2. The hydrostatic pressure in the capillaries exceeds the colloid osmotic pressure of the plasma proteins.
3. Factors which play a secondary part in the production of oedema include increased capillary permeability secondary to anoxaemia and reduction in colloid osmotic pressure. The latter may be due to hypoproteinaemia resulting from anorexia, malabsorption from venous congestion in the intestine, defective

metabolism from congestion of the liver and perhaps to loss of protein in the urine or in transudates.

In right ventricular failure, oedema usually occurs first in the dependent parts of the body, i.e. it is found round the ankles if the patient is up and about or in the sacral region if confined to bed.

HYDROTHORAX is usually bilateral, but may be confined to one side.

ASCITES is usually a later manifestation of failure than peripheral oedema but tends to be especially prominent in constrictive pericarditis and whenever prolonged cardiac failure has led to cirrhosis of the liver with portal hypertension.

ENLARGEMENT OF THE LIVER. The inability of the right ventricle to deal with the increased venous return to the heart is also reflected in engorgement of the liver which becomes enlarged and tender. In the early stages there may be abdominal pain from stretching of the capsule. Anorexia and abdominal distension may be troublesome features of portal venous engorgement.

RENAL FEATURES. A reduction in the secretion of urine (oliguria) commonly accompanies severe cardiac failure. The reabsorption into the blood of tissue oedema which has accumulated during the day and the excretion of this fluid by the kidneys is facilitated by the recumbent posture. Nocturia is therefore a common complaint in cardiac failure, particularly in ambulant patients. Proteinuria is frequent.

Treatment of Cardiac Failure

General Principles. Whenever possible, treatment should be directed towards the underlying cause, e.g. thyrotoxicosis or hypertension. Certain conditions such as congenital defects, acquired disease of the valves and constrictive pericarditis are often amenable to surgical treatment.

Rest

Rest is of fundamental importance in the management of every patient with cardiac failure and confinement to bed is often necessary. When breathlessness is extreme, the patient is compelled to sit up and it may be found that sitting in a chair is more comfortable than sitting up in bed. Oedema then tends to collect in the legs rather than in the lungs and this may be an advantage when fluid retention is difficult to combat. A bedside commode or sani-chair should be used whenever possible as this involves considerably less strain than the use of a bedpan. Confinement to bed has other disadvantages, notably the risk of venous thrombosis in the lower limbs and its attendant dangers. The muscles weaken and hypostasis in the lungs predisposes to pneumonia. Mobilisation should gradually be instituted as the cardiac failure comes under control and progressively increased as the patient improves.

Digitalis

Digitalis is still a very useful drug in the treatment of cardiac failure. It is most effective in patients with rapid atrial fibrillation, but it is also of value when sinus tachycardia accompanies failure. It is used in the treatment of paroxysmal atrial tachycardia or flutter and also for the prevention of these conditions. Digitalis will be most effective when the left ventricle is failing as from hypertension or ischaemic heart disease. In right ventricular failure due to disorders of the pulmonary circulation its clinical benefits are more difficult to assess, but it should not be withheld on this account. It is not indicated in the treatment of uncomplicated sinus tachycardia or constrictive pericarditis, and is contraindicated in ventricular tachycardia, and in partial heart block because the degree of block may be increased.

ACTIONS OF DIGITALIS

Improvement of Myocardial Efficiency. The strength of contraction is increased by direct stimulation of the myocardium. The dilated ventricles empty more completely, the cardiac output is increased and the venous pressure is lowered. The work of the heart is more efficient in that relatively less oxygen is used by the myocardium for a given amount of work. The improved renal blood flow causes a diuresis in patients with heart failure.

Slowing of the Heart Rate. Digitalis slows the heart by direct depression of the conducting tissues and by vagal stimulation. Improvement of function and slowing of rate are closely related.

ADMINISTRATION OF DIGITALIS

Digoxin is the best preparation for all purposes because it is chemically pure, well and quickly absorbed and can be given by mouth or injection. The aim of digitalisation is to control cardiac failure or a rapid ventricular rate and thereafter to give a maintenance dose for as long as is necessary. This will often be for life. Patients vary in their requirements but the average dose mainly depends on body weight. Urgent digitalisation by parenteral administration is rarely required because oral digoxin acts so quickly.

Full digitalisation can be achieved by oral dosage within a few hours, a day, three days or a week according to the degree of urgency. On occasion, e.g. for urgent control of a very rapid ventricular rate or severe pulmonary oedema intravenous injection is warranted and then digoxin, 1 mg for a 70 kg patient, may be given. The effect will be noticeable within 10 minutes. The effect of a large single dose of digoxin by mouth begins within an hour. Digitalisation within 24 hours can be achieved if necessary by giving digoxin, 1·5, 0·5, 0·5 and 0·5 mg at intervals of six hours.

When there is no urgency digitalisation over a few days or a week is to be preferred; toxic symptoms are thereby minimised. A suitable regime is to give digoxin, 0·5 mg t.d.s. the first day, 0·25 mg q.d.s. the next day, and thereafter 0·25 mg t.d.s. for a day or two until the heart rate is controlled and symptoms and signs of failure are relieved, or mild toxic symptoms ensue. Thereafter the usual maintenance dose is 0·25 mg once or twice daily.

Toxic Effects of Digitalis. Individuals vary considerably in their tolerance to digitalis. The toxic and therapeutic doses may be close. Toxic effects are a sign of overdosage and, if ignored, may prove serious. Toxicity is readily induced in the elderly who require relatively small dosage, and likewise in those with renal failure. When toxic symptoms develop, digitalis should be stopped for a few days and then resumed in a lower dosage.

The earlier clinical features of overdosage are anorexia, nausea and headache, followed by vomiting, occasionally diarrhoea and blurring of vision. Mental confusion may occur. The pulse rate may become unduly slow (under 60 beats per minute). Ventricular ectopic beats are a common occurrence and a warning to stop treatment for 24 hours. Coupled beats (p. 227) are characteristic of digitalis poisoning. It is important to listen to the apex beat because the presence of ectopic beats may be missed at the wrist. Before giving digitalis by injection or in large doses by mouth it should be ensured that the patient has not been taking the drug within the previous few days, or serious toxicity may result. Hypokalaemia may be responsible for hypersensitivity to digitalis and predisposes to cardiac toxicity. Patients receiving long term diuretic therapy are particularly at risk if potassium supplements are not prescribed (p. 250).

If administration of the drug is continued after toxic effects have appeared, various arrhythmias or defects of conduction may develop including in particular atrial tachycardia with block and ventricular tachycardia.

Symptoms such as anorexia, nausea and vomiting, may be due to cardiac failure and wrongly attributed to digitalis intoxication. Differentiation can usually be made by considering the amount of digitalis administered and other evidence of overdosage, or by estimation of blood levels. Occasionally, vomiting is of local and not central origin, in which case digitoxin may be better tolerated, 0·1 mg digitoxin being equivalent to 0·25 mg digoxin.

Diuretics

The applied pharmacology and dosage of the various diuretics in use at the present time is discussed on pages 195-196. They are effective in both left- and right-sided heart failure and may protect the patient from attacks of nocturnal dyspnoea.

Regular weighing of the patient is a good guide to the early recognition of fluid retention or fluid loss. Apart from obvious oedema, patients can often tell when they are in need of a diuretic by a feeling of increasing tightness in the chest or abdomen and by dyspnoea.

Diuretics should be given orally provided nausea or vomiting does not prevent their administration. In acute left ventricular failure parenteral administration is indicated.

The *thiadiazine group* of drugs (p. 195) which includes chlorothiazide, hydrochlorothiazide, bendrofluazide, hydroflumethiazide and polythiazide has become established as the first choice, but the more expensive drugs frusemide and ethacrynic acid are superior when speed of action is important. In terms of diuretic effect and toxicity there is little to choose between the thiadiazine drugs and usually the choice should be determined by cost. If given over a prolonged period, depletion of body potassium with all its possible consequences (p. 190) is liable to be produced. Hence it is essential to prescribe a supplement of potassium when oral diuretics are given more than twice a week. The daily prophylactic dose is 3 g of potassium chloride or equivalent potassium salt. Salt intake should be restricted in order to minimise the dosage of oral diuretics.

Chlorthalidone (p. 195) has a gentler but much longer duration of action than chlorothiazide and its derivatives and when there is no urgency for a prompt diuresis it may be the drug of choice.

Frusemide and *ethacrynic acid* (p. 195) are much more potent and rapidly acting than other diuretics. Diuresis is extremely rapid in onset and is generally completed within six hours. This is a great advantage for cases urgently requiring treatment, e.g. pulmonary oedema, but a disadvantage in chronic cardiac failure in which a more gentle action may be desirable. Both frusemide and ethacrynic acid may cause an excessive loss of potassium so that dosage must be carefully regulated and supplements of potassium given (p. 190). Sodium depletion can also be induced (p. 187).

Triamterene and *amiloride* are less potent diuretics but have the advantage of producing a relatively small excretion of potassium. They are best given in combination with a small dose of another oral diuretic.

Spironolactone. Spironolactone inhibits the action of aldosterone (p. 655) and thus promotes sodium loss and potassium retention. The dose is 25 mg four times a day. It is of only limited value but is sometimes of use when intractable oedema is present. The drug is ineffective alone and should be given in combination with another diuretic.

Salt Restriction

The accumulation of sodium in the body is mainly responsible for the retention of water and oedema. The average daily intake of salt is normally about 10 g; if no salt is added at table it is about 5 g and if salt is withheld from cooking about 3 g. Special diets can be devised which contain less than 1 g of sodium (Diet 8, p. 998), but to achieve this it is necessary to take salt-free butter or margarine and salt-free bread. Sodium-free 'salt' is available for table use. Such severe restrictions are necessary only if oedema cannot otherwise be controlled and this is rarely the case since the introduction of the oral diuretics. For practical purposes if no salt is added at table or in cooking and a diuretic is given there need be no limitation of the amount of fluid taken by mouth.

Care must be taken not to prescribe medicine containing sodium, e.g. antacids, and to avoid baking powder in cooking. Therapy liable to cause sodium retention is contraindicated, e.g. carbenoxalone or phenylbutazone.

Other Measures

Diet. Weight reduction is advisable in obese patients. An adequate vitamin content should be ensured, particularly as regards the B group and vitamin C. Diet No. 7 (p. 997) is suitable for a case of severe cardiac failure.

Oxygen. The indication for giving oxygen in cardiac disease is arterial oxygen undersaturation, e.g. from cardiac failure with pulmonary congestion, from associated disease of the lungs or in severe myocardial infarction. The need for oxygen may be indicated by the presence of central cyanosis which, however, may be masked by shock or anaemia; considerable undersaturation may be present without detectable cyanosis. Oxygen must be given with caution in chronic pulmonary disease (p. 332). For details of administration see page 331.

Reduction in Venous Return. This may be of value in acute pulmonary oedema and may be achieved by venesection or application of sphygmomanometer cuffs to three limbs at one time with the removal of one cuff to the fourth extremity every 15 minutes.

Paracentesis. Pleural effusions and ascitic fluid should be removed whenever large enough in volume to contribute to dyspnoea or to cause marked discomfort.

Treatment of Paroxysmal Dyspnoea and Acute Pulmonary Oedema

The first essential is to place the patient in the upright sitting posture in order to drain as much blood as possible into the dependent parts of the body and increase the vital capacity. Morphine, 10-15 mg, should be injected, preferably intravenously together with cyclizine to reduce the liability to vomiting which morphine may cause. The response is usually dramatic. Oxygen should be administered in high concentration if central cyanosis is present. In patients with left ventricular failure (who have not been taking digitalis for 14 days) digoxin, 1 mg, should be given intravenously. A potent diuretic such as frusemide should also be given intravenously. The slow intravenous injection of aminophylline, 0·5 g, is useful if bronchospasm is present.

ACUTE CIRCULATORY FAILURE

Acute Cardiac Failure

Acute cardiac failure may result from myocardial infarction, massive pulmonary embolism, paroxysmal tachycardia, myocarditis or cardiac tamponade. The principal factor is a severe reduction in cardiac output.

The clinical picture of acute cardiac failure is similar to that which occurs in peripheral circulatory failure. The term ‘shock’ is often applied to the symptoms and signs of acute circulatory failure, whether they are of cardiac origin (‘cardiogenic shock’) or from some other cause (‘peripheral circulatory failure’).

Peripheral Circulatory Failure

The fundamental basis of peripheral circulatory failure is a decrease in the circulating blood volume, and hence a generalised tissue anoxia. As a result compensatory mechanisms are brought into play to try and maintain an adequate circulation to the more vital parts of the body, such as the heart and brain and the maintenance of an adequate blood pressure. This is achieved by vasoconstriction in relatively non-essential parts of the body such as the skin and the splanchnic area.

Aetiology. Peripheral circulatory failure arises from a reduction in effective blood volume due to:

1. *Haemorrhage*. This may result from accidents, operations, gastrointestinal disease, ruptured ectopic pregnancy and ante- or post-partum haemorrhage.
2. *Trauma and Burns*. These conditions may cause very considerable loss of fluid into the tissues.
3. *Neurogenic Shock*. This condition occurs suddenly from reflex vasodilatation with consequent pooling of blood in the small vessels, particularly in the splanchnic area, deficient venous return to the heart and hence reduced cardiac output. It may be seen in various clinical conditions, which are usually accompanied by pain, e.g. perforation of a peptic ulcer, a blow on the 'solar plexus' or testicles, acute pancreatitis or severe pain from any other cause. In some of these conditions there may also be a loss of fluid, e.g. into the peritoneal cavity.
4. *Miscellaneous Causes*. In some forms of shock there is no loss of blood or plasma, but reduction in circulating blood volume is due to loss of fluid and electrolytes. This occurs in diarrhoea, vomiting, diabetes and Addison's disease.

Peripheral circulatory failure may also result from severe bacterial infections, particularly with Gram-negative organisms (p. 106), but the mechanism is not clear.

Anaphylactic shock is believed to result from direct impairment of vascular tone and permeability (p. 30).

Clinical Features. There is apathy or restlessness, a pale cold clammy skin, a rapid pulse of poor volume, hypotension and oliguria. If severe shock is prolonged it becomes irreversible and the cardiac output and blood pressure continue to fall despite all methods of treatment.

Prophylaxis. Much can be done to prevent the onset of shock by gentle handling of injured parts and by protection from cold; by prompt attention to the control of haemorrhage and pain; by minimising the loss of fluid from the body and the early correction of dehydration and electrolyte loss. Early diagnosis is all-important.

Treatment. Treatment should be directed towards the cause of the circulatory failure whenever possible, e.g. a bleeding vessel, perforated ulcer or diabetes. Pain must be relieved, e.g. by morphine. Warmth, e.g. by blankets, should be applied to conserve body heat but sweating should be avoided, since this will result in further fluid loss. Raising the foot of the bed will facilitate the venous return to the heart and help to maintain the cerebral circulation. For severe cases of shock with marked hypotension the intravenous infusion of hydrocortisone, metaraminol or noradrenaline may be used but the last two are of no value if vasoconstriction is maximal.

Transfusion of blood is a most important measure in the treatment of shock due to loss of blood. Transfusion of plasma may be given when blood is not available and in the treatment of burns. Plasma substitutes, e.g. dextran, are valuable whenever blood or plasma is not available.

DISEASES OF THE HEART VALVES

The descriptions of all forms of valvular disease have been grouped together because the manifestations are largely independent of the aetiology.

Since the medical treatment of the sequelae of valvular disease has been described under Cardiac Failure, reference to treatment in this section will be confined to the value of surgical procedures.

Aetiology. The principal cause of valvular disease is rheumatic endocarditis. This most commonly affects the mitral valve, next the aortic valve, comparatively infrequently the tricuspid valve and very rarely the pulmonary valve. Syphilis may cause aortic regurgitation secondary to dilatation of the aorta; it does not produce aortic stenosis. Congenital lesions are responsible for most cases of pulmonary valvular disease, some cases of aortic disease and occasionally for tricuspid disease. Infective endocarditis may be superimposed on rheumatic and congenital lesions and cause further damage. A cusp may be ruptured during surgical treatment or occasionally by external trauma. A diseased valve may be narrowed (stenosed) or may fail to close adequately and thus permit of regurgitation of blood. The term incompetence may be used synonymously with regurgitation but the latter is preferable as a stenosed valve is not obviously ‘competent’. Regurgitation may be present without structural changes in the cusps, e.g. from dilatation of the mitral valve ring in left ventricular failure, the tricuspid valve ring in right ventricular failure, the pulmonary valve ring in pulmonary hypertension or the aortic valve ring in aortic aneurysm or dilatation.

Mitral Valve Disease

Pathology. Rheumatic fever is responsible for most cases of mitral valvular disease. Rheumatic endocarditis leads to inflammation, thickening, fibrosis and deformity of the valve cusps, the chordae tendineae and the valve ring. This leads to varying degrees of imperfect closure and of narrowing of the valve. Adhesions of the cusps, rigidity and calcification may lead to a narrowing of the orifice and sometimes to a slit-like ‘buttonhole’ aperture. Shortening of the chordae may produce a ‘funnel-shape’ which further accentuates the narrowing.

Mitral Regurgitation

Most cases of mitral regurgitation result from rheumatic fever. Other causes include rupture of chordae or a papillary muscle, erosion of a cusp from infective endocarditis or widening of the A-V ring from dilatation of the left ventricle or rarely from congenital malformation.

In mitral regurgitation the left atrial volume increases with ventricular systole and the left ventricle is overfilled during diastole but its output per beat into the aorta is unchanged until left ventricular failure develops.

Symptoms. Often the left ventricle can compensate for the increase in diastolic volume and there will be no symptoms. In more severe cases symptoms and signs of cardiac failure are similar to those of mitral stenosis.

Signs. 1. A pansystolic murmur maximal at the apex and often conducted towards the left axilla. The murmur may be accompanied by a thrill.

2. In contrast to mitral stenosis the first heart sound is weak or absent.

3. Enlargement of the left atrium. This can only be detected radiologically.

4. Enlargement of the left ventricle, which may be felt as a distinct thrust at the apex of the heart or seen radiologically.

5. Left ventricular hypertrophy may be demonstrated by electrocardiography.

Differential Diagnosis of Apical Systolic Murmur. The characteristic murmur of mitral regurgitation is pansystolic, loudest at the apex and often well heard towards the left axilla and lung base. The murmur is usually blowing or harsh in character and may be accompanied by a systolic thrill. The intensity of the murmur is an unreliable guide to the severity of the valvular defect but usually the louder the murmur the more likely is it to be significant.

It is important to appreciate that an aortic systolic murmur is often well heard or even best heard at the apex; likewise if the heart is enlarged and rotated, a tricuspid systolic murmur may be loudest in this region.

The discovery of an apical systolic murmur without other evidence of heart disease is a common clinical experience and should always be followed by a thorough examination. If the individual is otherwise well, if there is no history of rheumatic fever or evidence of enlargement of the heart, and if blood pressure is normal and there are no other abnormalities, the murmur can, from the practical point of view, be ignored. It is most important that unwarranted restrictions should not be imposed or anxiety engendered.

Surgical Treatment. In some cases, the valve can be repaired but a prosthesis is usually required. Open heart surgery is necessary; the mortality of the operation in most centres is 5-15 per cent. Long-term results are often unsatisfactory because of associated myocardial damage.

Mitral Stenosis

In moderate or more severe cases of mitral stenosis, pressure in the left atrium is raised and leads to pulmonary venous hypertension and congestion and, in time, to hypertrophy, dilatation and eventually failure of the right side of the heart. Atrial fibrillation is a common complication which aggravates the haemodynamic effects.

Symptoms. Pulmonary congestion causes a decrease in compliance and consequently increases the work of breathing and is responsible for the subjective sensation of dyspnoea. Attacks of acute pulmonary oedema may occur with exercise, emotion or tachycardia from any cause such as the onset of atrial fibrillation, or with pregnancy. Palpitation may be distressing and cough may result from pulmonary congestion. Haemoptysis may occur from rupture of bronchial veins or from pulmonary infarction. Important complications include systemic and pulmonary embolism.

Signs. 1. Peripheral cyanosis is attributable to the reduced skin blood flow. The pulse volume is small when there is a reduced stroke volume. A dusky flush over the cheek-bones ('malar flush') is common.

2. The apical impulse is often 'tapping' in quality and corresponds to the loud first sound. A right ventricular thrust may be felt behind and to the left of the lower sternum and in the epigastrium.

3. A diastolic thrill is sometimes palpable at the apex.

4. A diastolic murmur maximal at, or confined to, the region of the apex beat is the hallmark of mitral stenosis. The murmur may be pre-systolic in time or fill most of diastole with apparent pre-systolic accentuation. It is usually low-pitched and rumbling in quality and best heard with a bell stethoscope lightly applied and the patient lying on the left side. In early cases it may be heard only if the heart rate is increased, e.g. by exercise. The presystolic accentuation of the murmur is dependent on atrial systole and hence disappears with the onset of atrial fibrillation.

5. The first heart sound at the apex is characteristically loud and sudden. The second heart sound at the base may be accentuated from pulmonary hypertension. An added sound, the 'opening snap', coinciding with the opening of the mitral valve, is usually heard immediately preceding the mid-diastolic murmur.

6. Enlargement of the left atrium can readily be seen on radiological examination, especially in the right oblique position, in which it will be seen projecting backwards and indenting the barium-filled oesophagus (Fig. 36, p. 224). Later enlargement of the pulmonary artery and of the right ventricle occurs. Pulmonary venous congestion and horizontal lines from dilatation of the lymphatics in the costophrenic angles are often present. Calcification of the mitral valve may be observed.

7. Left or right atrial hypertrophy and right ventricular hypertrophy may be detected by electrocardiography.

Surgical Treatment. Mitral valvotomy not only reduces the back pressure on the lungs and hence by relieving pulmonary congestion alleviates dyspnoea but also permits of a greater increase in cardiac output especially on exertion. The degree of mechanical obstruction at the mitral valve is, however, rarely the only factor of importance in mitral stenosis. The amount of myocardial damage, the presence or absence of other valvular defects, the occurrence of narrowing in the pulmonary arterioles and the changes in the lungs which result from prolonged congestion all contribute to the overall clinical situation. However, the mechanical factor is frequently predominant.

The most suitable patients for operation are those with uncomplicated mitral stenosis, in sinus rhythm and with no great enlargement of the heart. The possibility of surgical treatment should be considered whenever there is a considerable disability or evidence of progression of symptoms and signs. However, so many factors have to be considered which require special experience that it is best for all patients who have signs of mitral disease to be referred to a cardiologist and thereafter to have a periodical review. Pulmonary oedema and recurrent haemoptysis are strong indications for operation, while atrial fibrillation is a disadvantage but not a contraindication. Not only does atrial fibrillation mean that the myocardium has been involved by the rheumatic process but also that clot is more likely to be formed in the atrium than if normal rhythm is present and consequently there is an increased risk of systemic embolism. Some cases are complicated by mitral regurgitation and others by aortic valvular disease and it is important to decide which of these defects is dominant. Remarkable clinical improvement can be achieved by this operation in suitably selected cases and this usually persists for some years. However, many patients eventually require a second valvotomy for re-stenosis. If the valve is severely damaged it can be replaced by a prosthesis. It must be remembered that surgical treatment is but an incident in the relentless progress of rheumatic heart disease whether from activity of the rheumatic process or from the subsequent progressive fibrosis.

Aortic Valve Disease

Aortic Regurgitation

Aetiology. Most cases are due to rheumatic fever but some to infective endocarditis, syphilitic aortitis, congenital malformation or occasionally trauma. A mild degree of functional regurgitation may be secondary to hypertension or to atherosclerosis of the aorta.

Pathology. In rheumatic cases there is a thickening and shortening of the cusps, and stenosis often co-exists. Syphilitic aortic regurgitation results from dilatation of the aortic valve ring.

Symptoms. Owing to the ability of the powerful left ventricle to deal with the reflux of blood which occurs in diastole, compensation may be excellent for many years. In time, left ventricular failure occurs and progressive dyspnoea on exertion is soon followed by paroxysmal dyspnoea at rest, orthopnoea and finally right ventricular failure.

Signs

1. The characteristic and most important sign of aortic regurgitation is a high-pitched, blowing, early diastolic murmur commencing immediately after the second heart sound and best heard down the left sternal edge using a diaphragm chest piece firmly applied and with the patient standing or sitting and the breath held in expiration. A blowing systolic murmur from the increased stroke volume is a common accompaniment.

2. Enlargement of the left ventricle leads to displacement of the apex beat downwards and to the left and to a heaving impulse.

3. Low diastolic blood pressure with high pulse pressure.

4. Peripheral signs if the regurgitation is free:

   (*a*) Collapsing radial pulse. There is an abrupt upstroke with sudden impact against the examining finger and a rapid falling away or 'collapse'.
   (*b*) Visible arterial pulsation, e.g. in the carotid arteries.
   (*c*) Associated peripheral vasodilatation gives rise to pink and warm extremities and to capillary pulsation, e.g. in the nail beds.

5. Radiography will show the degree of left ventricular enlargement and the electrocardiogram may show the pattern of left ventricular hypertrophy.

Surgical Treatment. If there are symptoms of left ventricular failure or signs of progressive left ventricular enlargement or hypertrophy the valve should be replaced.

Aortic Stenosis

Aetiology. Some cases are due to rheumatic fever, usually in association with other valvular lesions. Aortic stenosis with calcification of the valve often occurs as an isolated lesion as a result of calcification in a congenital bicuspid valve. An aortic systolic murmur from a sclerotic valve but without significant obstruction is a frequent finding in the elderly.

Symptoms. The clinical features will depend on the degree of narrowing and the presence or absence of lesions of other valves.

Mild cases of stenosis are relatively frequent but often unrecognised and in the compensated phase symptoms may be entirely absent. When left ventricular failure occurs its symptoms and signs are similar to those occurring in aortic regurgitation.

In addition, faintness, dizziness, syncope on exertion and anginal pain on exertion are characteristic manifestations and sudden death is liable to occur. Such symptoms are due to myocardial or cerebral ischaemia.

Signs

In established cases some or all of the following signs are usually present:

1. The apical impulse is thrusting in quality as a result of left ventricular hypertrophy.

2. A systolic thrill maximal in the same area as the murmur and likewise transmitted into the neck is a common but not invariable accompaniment. As with the diastolic murmur it is best appreciated with the patient leaning forward and the breath held in expiration.

3. A harsh murmur maximal in mid-systole and best heard either to the right of the upper sternum, at the left border or even at the apex. It may be transmitted into the carotid arteries.

4. Faint or absent aortic component of the second sound.

5. An aortic diastolic murmur is often present but without peripheral signs of free aortic regurgitation, i.e. undue arterial pulsations.

6. Pulse of small amplitude and rising slowly to a delayed peak.

7. Lowered systolic blood pressure and decreased pulse pressure.

8. Left ventricular enlargement or hypertrophy may be confirmed by radiography and electrocardiography.

9. Calcification of the aortic valve may be seen on the radiograph and particularly with an image intensifier screen.

The severity of aortic stenosis must be judged by symptoms and the degree of left ventricular hypertrophy. Auscultatory findings, pulse volume and blood pressure readings may be misleading.

Surgical Treatment. If there are symptoms of left ventricular failure or signs of progressive left ventricular hypertrophy, or if the left ventricular pressure is high with a large systolic gradient across the valve (50 mm Hg or more), surgical treatment with replacement of the valve is advisable.

Pulmonary Valve Disease

Pulmonary Stenosis

This is almost always congenital in origin and may occur as an isolated lesion or in association with a ventricular septal defect, particularly as part of the tetralogy of Fallot (p. 296). The principal features are a loud systolic murmur and thrill and right ventricular hypertrophy. A pulmonary systolic murmur from high blood flow across a normal valve is frequently audible in children, in pregnancy and in hyperkinetic states such as anaemia or thyrotoxicosis or with a left-to-right shunt particularly between the atria. It can be distinguished from that of pulmonary stenosis by the softness of the murmur and the absence of right ventricular hypertrophy.

Pulmonary Regurgitation

This usually results from pulmonary hypertension, e.g. in mitral stenosis. An early diastolic murmur can be heard to the left of the upper sternum (Graham Steell murmur). Dilatation of the pulmonary artery and hypertrophy of the right ventricle are associated. Most diastolic murmurs heard in this area originate at the aortic valve and can often be distinguished by the presence of other signs of aortic regurgitation.

Tricuspid Valve Disease

Aetiology. Most cases of tricuspid disease are rheumatic in origin and associated with severe mitral stenosis and often aortic valve disease as well. Tricuspid regurgitation also frequently results from right ventricular dilatation when this chamber fails because of pulmonary stenosis or hypertension. Occasionally, tricuspid disease is of congenital origin.

Symptoms and Signs. Both tricuspid stenosis and regurgitation lead to the features of right-sided cardiac failure with jugular venous distension, hepatic enlargement, peripheral oedema and ascites. There is often relatively little dyspnoea or orthopnoea in spite of co-existent mitral stenosis, owing to the diminished output of the right ventricle into the lungs. If sinus rhythm is maintained, there is electrocardiographic evidence of right atrial hypertrophy. Dilatation of the right atrium can be detected radiographically.

In tricuspid stenosis, there is usually a prominent 'a' wave in the jugular venous pulse. The murmurs resemble those of mitral stenosis in being mid-diastolic and pre-systolic but differ in being maximal at the lower left sternal edge and increasing in intensity on inspiration.

In tricuspid regurgitation, there is a large systolic pulsation in the jugular veins due to the backflow of blood during systole. The systolic murmur of tricuspid regurgitation is maximal at the lower sternal region and is accentuated by inspiration.

The signs of tricuspid valve disease are often overshadowed by mitral or aortic valve disease. On the other hand, it is not uncommon for tricuspid stenosis and incompetence to obscure the signs of mitral stenosis.

Treatment. Repair, valvotomy or replacement may be necessary when tricuspid valve disease is severe. Usually, there is concomitant mitral valve disease which also requires surgical treatment.

Rheumatic Fever

The incidence of rheumatic fever is greatest in childhood and adolescence, 90 per cent of cases commencing between the ages of 5 and 15. In recent years the incidence in the Western World has fallen very considerably but the disease remains common in Asia, Africa and Eastern Europe. Recurrences are frequent unless prophylactic treatment is given (p. 262). Mild and subclinical forms occur and about half the patients who are found to have valvular disease of the heart of rheumatic origin give no history of rheumatic fever.

Aetiology. The precise cause of rheumatic fever is unknown. However, there is much evidence that it is related to infection with Group A β-haemolytic streptococci, probably on the basis of an antigen common to the heart and the streptococcus (p. 38). The disease is often preceded by tonsillitis or pharyngitis one to three weeks before. Rheumatic fever tends to occur in families but this may be due to environment rather than to heredity. It commonly affects the lower income groups and town dwellers. Poor housing and over-crowding are important factors.

Pathology. The connective tissues of the body are principally involved. Joints, muscles, tendons, heart valves, subcutaneous tissues and blood vessels are all affected. In the exudative stage there is hyperaemia, oedema of the collagen tissue and infiltration with leucocytes. The hallmark of rheumatic fever is the Aschoff nodule, which may be found in the interstitial tissues of any part of the heart, most frequently under the endocardium and in close relation to small blood vessels. Its microscopic appearance is that of a central area of necrosis surrounded by small round cells, histiocytes and giant cells.

Clinical Features

ONSET. The onset may be sudden with pain, swelling and stiffness in one or more joints, fever, sweating and tachycardia, or the onset may be insidious with fatigue, malaise and loss of weight.

FEVER. Fever is usual in acute attacks but variable in degree and duration and much influenced by the administration of salicylates which have a marked antipyretic effect. Sweating may be profuse and tends to be accentuated by salicylates. Other accompaniments of fever, such as anorexia, furred tongue, constipation and proteinuria, are often present.

TACHYCARDIA. This tends to be out of proportion to the degree of fever and may persist after the latter has settled. The sleeping pulse rate will differentiate tachycardia due to anxiety or excitement, and this observation is useful in deciding when more physical activity can be permitted.

POLYARTHRITIS. This manifestation is more marked in adults than in children. The large joints are principally affected, e.g. knees, ankles, shoulders and wrists, but almost any joint may be involved. Characteristically there is a migrating polyarthritis, that is to say the pain tends to move from one joint to another, one improving as another becomes worse. In severe cases the joints become hot, swollen, red and very tender. The synovium and periarticular tissues are principally involved. Sterile effusions may develop. However, there are no residual effects in the joints once the acute attack is over.

CARDITIS. This is characterised by endocarditis, pericarditis or myocarditis or by any combination of these. Carditis may occur without any other evidence of rheumatic fever.

ENDOCARDITIS. In the early stages this may be suspected from diminished intensity of the first heart sound or from the development of a systolic murmur. A transient mitral diastolic murmur may be heard. There may, of course, be evidence of previous rheumatic infection, e.g. mitral stenosis or aortic incompetence.

PERICARDITIS (p. 287). Pericarditis may be suspected as a complication when there is a recrudescence of fever with the development of malaise, restlessness and pallor. Retrosternal or precordial pain is common and pericardial friction may be heard. An effusion may develop. Characteristic changes may occur in the electrocardiogram (p. 223). Pericarditis is not in itself a serious manifestation of rheumatic fever, but its association with severe myocarditis is almost invariable.

MYOCARDITIS. This may be assumed to be present if there is endocarditis or pericarditis, but its clinical manifestations may be difficult to recognise. Active myocarditis is suggested by undue tachycardia, decreased intensity of the first heart sound, increasing enlargement of the heart, evidence of cardiac failure and abnormalities in the electrocardiogram (prolongation of the P-R and Q-T intervals).

RHEUMATIC NODULES. Rheumatic nodules are seen far less frequently than 20 years ago because rheumatic fever is less common and less severe. They occur most often in childhood and their principal importance lies in the almost invariable association with active carditis. They are situated subcutaneously, are painless, not attached to the skin and tend to occur over bony prominences such as elbows, backs of hands, knees, malleoli, skull, scapulae and vertebrae or be attached to tendons.

ERYTHEMA MARGINATUM (ERYTHEMA ANNULARE). Reddish patches appear mainly on the trunk and rapidly enlarge to form irregular crescent shapes which join together to form larger areas. The margins are slightly elevated. The lesions tend to disappear and reappear over a short period of time.

ERYTHEMA NODOSUM. Erythema nodosum is an occasional manifestation of rheumatic fever or streptococcal infection, other causes being tuberculosis and sarcoidosis.

BLOOD. A polymorph leucocytosis of 10,000 to 15,000 cells per c. mm is common in the acute stage and hypochromic anaemia often accompanies active rheumatic infection. A raised erythrocyte sedimentation rate is usually present in the active stages and may persist as evidence of activity of the rheumatic process when all other manifestations have subsided. A high A.S.O. (anti-streptolysin 'O') titre rising or raised to above 300 units provides evidence of recent streptococcal infection.

CHOREA (SYDENHAM'S CHOREA). There is no doubt about the close relationship of chorea to rheumatic fever in many cases. The majority of children with chorea either show evidence of rheumatic valvular disease or develop such evidence subsequently. The clinical features suggest involvement of the basal ganglia, and when the opportunity for study has occurred changes suggesting an encephalitis in this region of the brain have been found, although they are surprisingly mild. The clinical features of chorea are described under the Diseases of the Nervous System (p. 877).

Progress. The active and inactive forms of rheumatic heart disease must be distinguished. Persistent activity is suggested by the presence of fever, tachycardia, anaemia, changing cardiac signs, failure to gain weight, a raised blood sedimentation rate and abnormalities in the electrocardiogram. Activity implies progressive damage to the heart by the rheumatic process. It may be followed by a period, probably over several years, when the contraction of fibrous tissue leads to increasing deformity of the involved valves. Thereafter, unless further attacks of rheumatic infection occur, deterioration is due to the mechanical effects of valvular disease, which in time may lead to failure of the heart muscle.

Differential Diagnosis. The diagnosis of rheumatic fever in the absence of any cardiac abnormality must sometimes be considered when fever and joint pains are the principal manifestations. It is a fallacy to assume that rheumatic fever may be excluded because only one joint is involved. It is, however, true that rheumatic fever is unlikely to be responsible for joint symptoms which are not markedly alleviated by salicylates within 48 hours. The differential diagnosis of acute arthritis is discussed on page 770.

Prophylaxis. The problem of prevention, which is largely a social and economic one, is very important because there is no specific treatment for rheumatic fever, and very little can be done to mitigate the damage done to the heart. The heart is liable to be further affected in subsequent attacks. The incidence of relapses diminishes with age. Relapses may be largely prevented by giving a small dose of oral penicillin, phenoxymethylpenicillin 125 mg twice daily. Fortunately streptococci do not develop resistance to penicillin. Reactions, e.g. urticaria or joint pains, occasionally occur, in which case sulphadimidine, 0·5 g daily may be given instead.

Treatment

REST IN BED is essential throughout the active stage of the disease, i.e. until symptoms and fever have subsided, the sleeping pulse rate, white count and haemoglobin level have returned to normal, and weight is being regained. Thereafter, the return to activity should be gradual. The blood sedimentation rate is a useful guide to progress. Relapse may follow if the patient is allowed up before the rate is normal, but on occasion this rule may have to be ignored when a slightly raised rate persists.

DRUGS. *Penicillin* should be given for 7 to 10 days routinely at the start of treatment with the object of killing haemolytic streptococci in the nose and throat. Thereafter prophylactic penicillin should be given. If tonsillectomy is deemed to be necessary it should be carried out after the acute stage of the disease has subsided.

Salicylates are effective in combating fever and pain. Acetylsalicylic acid (aspirin) is preferable to sodium salicylate because it is better tolerated and has a greater analgesic effect. Aspirin soluble tablets B.P. are less liable to cause gastric irritation. It may be given every two hours for the first day or two and thereafter four-hourly with a double dose at night to save waking the patient. The total daily dose of aspirin is from 4 to 8 g depending on age and body weight. If sodium salicylate is prescribed the total daily dose for an adult varies from 6 to 10 g. This dosage should be continued until fever and symptoms have been controlled for at least 10 days and then gradually reduced. Should rheumatic manifestations return, treatment will have to be resumed. If toxic symptoms develop, the dose must be reduced and then maintained at the highest level which can be tolerated. Nausea, headache, dizziness, tinnitus and deafness are the early toxic symptoms, followed by vomiting, hyperventilation and mental symptoms. Occasionally haemorrhage may occur from hypoprothrombinaemia (p. 764).

There is little convincing evidence that salicylates influence the important cardiac complications, or materially shorten the course of the disease. Nevertheless they add to the patient's comfort and well-being.

Prednisolone. Clinical trials have shown that the combination of prednisolone with salicylates in high dosage is the most effective treatment for *severe* cases but has no effect on long-term results.

Other drugs may be needed for complications, e.g. cardiac failure.

CONVALESCENCE in a suitable environment will be required when the active stage is over and before return to school or work. Its duration will depend on the length of the preceding illness and the presence or absence of cardiac complications.

Sequelae. Rheumatic fever is often responsible for progressive cardiac damage even after the acute attack is over. Fibrosis and calcification of the valve structures may lead to stenosis or regurgitation, especially in the mitral and aortic valves. Myocardial fibrosis may also be an important factor in the eventual development of cardiac failure. There is usually a latent period of anything from five to fifty years between the acute attack and the development of major symptoms.

Until recently there were about 25,000 deaths from acute and chronic rheumatic heart disease in Britain each year. These formed about 20 per cent of all cardiac deaths. The incidence is falling, following that of rheumatic fever, and deaths are being postponed as the result of surgical treatment of valve disease. However, rheumatic fever is still the most common cause of heart disease under the age of 40.

Infective Endocarditis

Infective endocarditis should logically be classified on an aetiological basis depending on the organism responsible. In practice, however, it is divided into acute and subacute forms (of which the latter is the more frequent) largely because the clinical and pathological courses are usually distinctive and the responsible organisms are also different.

ACUTE INFECTIVE ENDOCARDITIS

As a result of modern treatment of acute infections by antibacterial drugs, acute infective endocarditis has become much rarer. It is a complication which results from an infection of the blood stream with virulent organisms, e.g. staphylococci, streptococci or pneumococci, and may attack healthy valves. High fever, sweats, rigors, wasting and septic emboli in various parts of the body are characteristic. Treatment with the appropriate antibiotic will be required, and in view of the seriousness of the condition the drug should be given in high dosage. The source of infection is usually apparent and often of a surgical nature, e.g. osteomyelitis or a septic abortion, and will itself require appropriate treatment.

SUBACUTE INFECTIVE ENDOCARDITIS

The subacute form mainly affects hearts previously rendered abnormal from rheumatic valvular or congenital heart disease. It is most often due to infection with non-haemolytic streptococci; these organisms are found in infected gums, teeth and tonsils. Transient bacteraemia frequently follows minor surgical procedures in such regions and although this is harmless in normal individuals the organisms may settle in the endocardium of abnormal hearts. A preceding history of dental extractions or, more rarely, urethral catheterisation may be obtained in some cases of infective endocarditis. Less frequently other organisms, e.g. staphylococci, brucellae, influenza bacilli or Coxiella (Q-fever) are responsible. Infective endocarditis used to be predominantly a disease of the young adult, but is now being seen increasingly in the elderly with calcific aortic valve disease or following surgical treatment or instrumental investigation of the urinary tract.

Clinical Features

Symptoms. Malaise, fatigue, anorexia, and pain in the joints.

General Appearance. Apart from pallor due to anaemia a curious earthy 'café-au-lait' complexion was not uncommonly seen in the late stages of the disease prior to the antibiotic era.

Persistent Fever. Infective endocarditis should always be considered in the differential diagnosis of a case of obscure fever, especially in a patient known to be suffering from heart disease.

Skin. Petechial haemorrhages into the skin and conjunctivae are frequent. Splinter haemorrhages may be seen under the nails. Osler's nodes are small, transient, painful, tender areas in the pulps of fingers or toes.

Clubbing of the Fingers. This is a common finding in long-standing cases but the changes are rarely gross.

Examination of the Heart will almost always show evidence of previous rheumatic valvular disease or some congenital defect.

Spleen. Moderate enlargement is usual.

Kidney. Microscopical haematuria is commonly found at some stage.

Peripheral Embolism. Emboli from the vegetations on the endocardium may lodge in spleen, kidneys, retinae, brain, limb or mesenteric vessels. The effects depend on the number and size of the emboli and may consist, for example, of sudden pain in the affected organs, blindness or segmental loss of vision, hemiplegia or a subarachnoid haemorrhage.

Blood. A progressive hypochromic anaemia occurs. There may be a moderate leucocytosis. The ESR is raised. A positive blood culture may be obtained in most cases, especially if pyrexia is present and if repeated specimens are taken. However, treatment should not be delayed for more than a day or two on this account if the diagnosis is reasonably certain on clinical grounds.

Prognosis. If the diagnosis is made early the infection can probably be eliminated in more than 90 per cent of cases by giving adequate doses of the appropriate antibiotic for a sufficient length of time. If, however, the diagnosis is delayed, which is not infrequently the case, the underlying cardiac disease may progress and the prognosis is much more serious.

Prophylaxis. Penicillin cover (p. 97) should be given to any individual with congenital or rheumatic heart disease, who has to have tonsillectomy or extraction of teeth, because these surgical procedures may well precipitate endocarditis. Prompt treatment of all infections is also important.

Treatment. Whenever possible the organism should be isolated by blood culture and its sensitivity to antibiotics assessed in the laboratory. The selection of the antibiotic, the assessment of dosage and the duration of treatment will depend on the results of the sensitivity tests and on the clinical response to treatment. If the organism is very sensitive, benzylpenicillin should be injected twice daily, usually for four to six weeks. If the organism is sensitive to penicillin and the temperature returns to normal within a few days benzylpenicillin may be replaced by phenoxymethylpenicillin given orally in a dose of 250 mg four to six hourly, in combination with probenicid, to ensure high blood levels. Larger doses of benzylpenicillin or the concurrent administration of streptomycin might be required for more resistant organisms. Depending on the bacteriologist's findings as regards sensitivity, other antibiotics or combinations of antibiotics may be necessary. In some resistant cases surgical treatment of the underlying cardiovascular defect may be necessary.

ISCHAEMIC HEART DISEASE

Ischaemic heart disease implies myocardial damage as a result of an inadequate coronary blood supply. In most cases, this is due to narrowing of the coronary arteries from atherosclerosis, but ischaemia of the myocardium may occur in a number of other conditions including:

(*a*) Aortic valve disease—in which the coronary blood flow may not be sufficient for the demands of increased left ventricular work.

(*b*) Syphilitic aortitis—in which the orifices of the coronary arteries may be obstructed although the vessels themselves are unaffected.

(*c*) Severe anaemia—in which the oxygen-carrying power of the blood is diminished.

(*d*) Paroxysmal tachycardia—in which the work of the heart is increased and the coronary blood flow is decreased owing to the shorter duration of diastole.

(*e*) Coronary embolism—in which the lumen of the vessel is obstructed, most frequently by a clot from the left atrium in patients with mitral stenosis and atrial fibrillation.

Pathogenesis. In the western world the prevalence of ischaemic heart disease is high and its incidence is increasing, especially in middle-aged and younger men but also in women some ten years older. In the rural areas of Asia and

Africa the condition is uncommon but is increasing in the cities. Migrants from developing countries to the western world are liable to change their ways of living and then develop atherosclerosis and its complications. The causes must therefore largely be environmental and hence potentially preventable. Population surveys and prospective epidemiological studies have led to the identification of certain predisposing factors, notably hyperlipidaemia, lack of physical exercise, cigarette smoking, endocrine changes, obesity, hypertension and emotional stress. It will be appreciated that most of these predisposing factors are 'unnatural' and related to western 'civilisation'. Evolving man is likely to have been active from dawn to dusk, was not obese and did not smoke. Emotion was likely to have been associated with physical activity rather than suppressed tension.

DIET AND HYPERLIPIDAEMIA. Since the lipids contained in atherosclerotic plaques are qualitatively similar to those circulating in the blood, the fat content of diet has received particular attention. Investigations into the incidence of ischaemic heart disease, the dietary intake of fat and the level of plasma lipids have been carried out in many countries and in most of them a significant correlation has been demonstrated between these three factors. It is possible to reduce the level of circulating cholesterol and triglyceride either by using a diet low in saturated fats, or by a diet in which unsaturated fats, e.g. vegetable oils from soya bean, maize or sunflower seed are substituted for saturated fats. The unsaturated fat diet is effective in lowering the level of serum lipids and also has the advantage that its ingestion may lead to a decrease in blood coagulability in contrast to a saturated fat diet which leads to increased coagulation. Thrombogenesis is obviously a matter of great importance in the presence of atherosclerosis. These diets can effectively reduce the plasma lipids but satisfactory evidence is still not available to prove that they can prevent the development of atherosclerosis or improve the prognosis of its sequelae, namely coronary, cerebrovascular and peripheral vascular disease.

Familial hyperlipidaemia is a highly important factor in the development of coronary disease in the young patient. Different types can be classified by lipoprotein characteristics and those associated with premature atherosclerotic disease recognised.

EXERCISE. With the mechanisation of industry and the development of the widespread use of the motor vehicle, the proportion of people who take vigorous exercise has declined. Also the proportion of sedentary workers, including office workers and business executives, has increased. Exercise improves myocardial vascularity and function and there is evidence that it lowers the plasma lipids, reduces platelet stickiness and increases fibrinolysis. Increased energy expenditure reduces obesity.

CIGARETTE SMOKING. Statistical data show that peripheral vascular disease and ischaemic heart disease, particularly myocardial infarction and sudden death, occur more frequently in cigarette smokers than in those who do not smoke.

ENDOCRINE FACTORS. The observation that ischaemic heart disease is rare in women before the menopause and that after the age of 55 the difference in the incidence between the sexes becomes less, suggests the possibility that oestrogens have some protective influence. Likewise the increased incidence of coronary thrombosis in patients with myxoedema, a disease in which the plasma cholesterol is raised, suggests that the secretion of the thyroid gland may also be of importance. Although the administration of oestrogens and thyroid hormones can lower the level of cholesterol in the plasma of both man and experimental animals, there is no evidence to show that the prognosis of ischaemic heart disease can be improved by their use.

Oral contraceptives probably enhance the chance of the development of myocardial infarction in women at risk, for other reasons, of the premature development of coronary atherosclerosis.

The association between atherosclerosis and diabetes mellitus is discussed on p. 703.

OTHER FACTORS. Hypertension, obesity and emotional stress are interrelated factors associated with ischaemic heart disease. Hypertension accelerates atherosclerosis by increasing infiltration of lipids through the arterial wall. It is potentiated by obesity which in turn discourages physical activity and may itself be an expression of psychological stress. Sustained anxiety has adverse effects on the blood pressure and sudden episodes of nervous tension frequently cause angina pectoris and may precipitate myocardial infarction.

Many factors are thus recognised as being involved in the pathogenesis of ischaemic heart disease and others are being investigated. Numerous patients die suddenly immediately after myocardial infarction and many who recover have advanced atherosclerosis. Significant control of this modern epidemic must depend on primary prevention whereby aetiological factors are removed or reduced in those at risk.

Clinical Features. Ischaemic heart disease may be manifested clinically by:

1. Sudden death
2. Angina pectoris
3. Myocardial infarction
4. Left ventricular failure
5. Arrhythmias
6. Defects of conduction.

Sudden death in patients with ischaemic heart disease may be due to coronary occlusion but this cannot always be demonstrated at post-mortem examination. In these cases death may have occurred because ischaemia has produced ventricular fibrillation. Angina pectoris is the term used to denote attacks of cardiac pain of short duration, without evidence of lasting damage to the myocardium. In myocardial infarction there is necrosis of an area of myocardium as a result of a severe inadequacy of the coronary circulation. Myocardial infarction is usually the result of coronary thrombosis or occlusion of a coronary artery by the rupture of an atheromatous plaque. Such events do not necessarily lead to infarction, however, because the collateral blood supply may be so good as to prevent death of the affected area. Sometimes, particularly in the elderly, diffuse coronary artery disease may lead to cardiac failure, arrhythmias or conduction defects rather than to angina pectoris or myocardial infarction.

Although it is convenient to describe these distinctive forms of presentation, differences between them are really matters of degree and any manifestation may be seen in the same patient at different times.

Angina Pectoris

Clinical Features. Pain is the dominant symptom in both angina pectoris and myocardial infarction. Although there are certain differences between the pain of angina pectoris and myocardial infarction, there are many similarities. In both cases the pain is characteristically felt behind the sternum or across the chest and is often described as being constricting or crushing in character. Sometimes there is no actual pain but rather a feeling of discomfort or an unpleasant sensation of pressure or weight. It may be described as 'only indigestion'; indigestion felt in the chest should always be suspect. The pain is rarely sharp, stabbing or knife-like. There may be no radiation or the pain may be referred down one or both arms, more commonly the left, sometimes to the fingers. The pain may extend into the throat, jaw or neck or pass into the shoulders, to the upper abdomen or through to the back.

In angina pectoris, the pain usually bears a quantitative relationship to exertion and forces the patient to stop; subsequently it passes away within a few minutes. The pain is more readily induced after meals and in cold weather. It may be precipitated by emotion. It is rapidly relieved by glyceryl trinitrate. In myocardial infarction, although the situation, distribution and quality of the pain is similar to that of angina pectoris, it is generally more severe and prolonged and is not relieved by rest or glyceryl trinitrate.

Diagnosis. The diagnosis of angina pectoris depends largely upon obtaining a characteristic history. Electrocardiograms recorded at rest are often normal, although they may show evidence of old myocardial infarction or minor abnormalities. The electrocardiogram on exercise, however, is usually abnormal if sufficient exercise is undertaken; the diagnostic feature is horizontal or downward-sloping depression of the ST segments.

Coronary angiography permits visualisation of the coronary arteries and usually shows major obstruction of at least one artery in patients with angina. However this potentially hazardous technique should be employed only when it is essential to establish the diagnosis or when coronary artery surgery is contemplated.

Treatment. General management is of major importance. The doctor must decide in each case how much to tell the patient, but usually it is best to explain that pain arises if the heart is stressed excessively. At the same time, the patient must be reassured as to the good prognosis if advice is taken. He should be encouraged to exercise, provided this does not provoke pain and to avoid, as far as possible, emotional conflicts and overwork. In most instances it is possible for the subject to continue in his occupation.

Attacks of pain can usually be prevented or abbreviated by the use of tablets of glyceryl trinitrate (trinitrin), 0·5 mg. These should always be carried so that one may be allowed to dissolve in the mouth as necessary. The patient should be told that trinitrin can be taken freely, for there are no important side-effects apart from headache, flushing and, rarely, syncope. Longer-acting nitrates have proved disappointing. On the other hand, propranolol (p. 235) and other similar drugs are often effective if the pain is not controlled by trinitrin but may provoke cardiac failure or exacerbate airways obstruction. Large doses must be given, such as 40-120 mg four times daily. Sedatives such as diazepam may be useful in reducing anxiety. Obesity and anaemia should be corrected if present. Meals should be small, eaten slowly and followed by a period of rest. Cigarette smoking should be given up.

Most patients, by adjustments in the way of life and the use of drugs, manage to adapt satisfactorily. In a few, however, symptoms are so serious as to be incapacitating. In such cases surgical revascularisation of the myocardium should be considered. A segment of saphenous vein may be used to link the aorta to the coronary artery beyond the obstruction. All three major coronary arteries may be treated. The operation is usually successful in relieving angina and provided left ventricular function is not severely impaired, the mortality should be less than 5 per cent. The effect of this procedure on long-term prognosis is not yet established.

Myocardial Infarction

Clinical Features. The prolonged severe pain of myocardial infarction and its lack of relief by rest and trinitrin usually differentiates it from that of angina pectoris. In addition, there is evidence of muscle necrosis such as fever, leucocytosis and an increased blood sedimentation rate. Blood pressure usually falls and may never recover its former level. There may be evidence of peripheral circulatory failure. A pericardial rub may be heard, usually on the second or third day.

Diagnosis. Characteristic changes appear in the electrocardiogram (Figs. 33, 34 and 35, p. 221). These include ST segment elevation and T wave inversion, accompanied in many cases by the appearance of broad Q waves. These changes occur in chest leads recorded over the affected area of muscle and may also be seen in the limb leads.

Necrosis causes a raised concentration in the serum of several enzymes including creatinine phosphokinase (CPK), aspartate aminotransferase (GOT) and lactate dehydrogenase (LDH) the latter being less specific. CPK and GOT rise in 3-6 hours and fall to normal in 2-7 days. LDH rises later but may remain elevated for 10 days or more.

The diagnosis is not always easy. The pain may be absent or atypical and in these cases the presenting feature may be a cerebrovascular disturbance as a result of a fall in cardiac output, an acute arrhythmia, heart block or the features of acute heart failure.

Differential Diagnosis. The pain of myocardial infarction may be mistaken for acute pericarditis (p. 287), pulmonary embolism (p. 282), dissecting aneurysm of the aorta (p. 303) or acute disease of the gastrointestinal tract, bile ducts or pancreas. Pain may arise in the oesophagus, from hiatus hernia or peptic ulceration. In addition, difficulty in diagnosis may be experienced with pain in the arms or chest as a result of disease involving the skeletal tissues or nerve roots.

Complications

CARDIAC FAILURE. Left ventricular failure occurs in a majority of cases of acute myocardial infarction and results in dyspnoea with crepitations in the lungs. In many cases this is slight, but occasionally severe pulmonary oedema is provoked. Right-sided heart failure is less common and usually takes some days to develop.

SHOCK. If major infarction has occurred, the patient may be pale, cold, sweating and mentally retarded, with hypotension and oliguria. If this clinical picture lasts for more than half an hour, the prognosis is bad (80 per cent mortality). Shock is normally associated with extensive myocardial damage but, in a few cases, it can be attributed to arrhythmias or heart block and may then be reversible.

ARRHYTHMIAS. These occur in the majority of patients with acute myocardial infarction and are responsible for a high proportion of the deaths. The most serious arrhythmia is ventricular fibrillation which causes death in 5 to 10 per cent of all cases of myocardial infarction. Other serious arrhythmias include ventricular tachycardia. These may be preceded by frequent ventricular ectopic beats indicative of a need for prophylactic therapy (p. 235).

DEFECTS OF CONDUCTION. Heart block in varied degree occurs in 5 to 10 per cent of all patients. Complete heart block is associated with a bad prognosis.

PULMONARY OR SYSTEMIC EMBOLISM. Pulmonary embolism may follow thrombosis in the right side of the heart or peripheral venous thrombosis, usually in the legs. Systemic embolism may occur if the infarct extends to the endocardial surface of the left ventricle.

RUPTURE OF THE WALL OF THE VENTRICLE, OF PAPILLARY MUSCLES, OR OF THE VENTRICULAR SEPTUM. Rupture of the wall of the heart usually leads to sudden death, whereas rupture of papillary muscles or ventricular septum results in the sudden onset of severe cardiac failure associated with a loud systolic murmur.

Treatment

RELIEF OF PAIN. The first step should be to relieve pain and anxiety. This is best achieved with morphine, 10-15 mg, which can be given intravenously in severe cases or by intramuscular or subcutaneous injection and repeated as required. Since morphine is liable to induce vomiting the drug should be given in combination with cyclizine (25-50 mg) or chlorpromazine (25-50 mg). Alternatively diamorphine (heroin) may be used in a dose of 5 mg by injection. If pain is less severe pethidine (50-100 mg), methadone (15-30 mg) or dihydrocodeine tartrate (30-60 mg) parenterally or by mouth may suffice.

SHOCK. The customary first-aid measures to combat shock are warmth, oxygen, raising the foot of the bed and the relief of pain. There is far from universal agreement about the value of any specific methods of treatment and, as already indicated, the prognosis of severely shocked patients is bad as it indicates extensive myocardial infarction. Various drugs have been tried with conflicting claims. These include hydrocortisone, 200 mg by intravenous injection, digoxin, 1 mg by intravenous injection, and vasoconstrictors. The last have proved ineffective in most cases because vasoconstriction is often already maximal, in which case they may be actually harmful.

OXYGEN. Oxygen should be given if there is evidence of pulmonary congestion or oedema or when there is shock.

TREATMENT OF ARRHYTHMIAS. Multiple ventricular ectopic beats, especially when superimposed on the preceding T wave, should be treated with lignocaine and other arrhythmias by the drugs described on page 233. Ventricular fibrillation should be treated by immediate electrical counter-shock. The management of cardiac arrest is discussed on page 239.

OTHER COMPLICATIONS. Cardiac failure should be managed in the usual way (p. 247) but because the ischaemic myocardium is particularly susceptible to digitalis toxicity, preparations of this drug must be given cautiously, particularly in the presence of potassium deficiency. Bradycardia should be treated with atropine and heart block may need electrical pacing.

REST IN BED. In recent years there has been a tendency to reduce the period of rest in bed and in patients without complications this can be limited to about four days. Thereafter, patients should be permitted to sit in a chair by the bedside for an hour or two each day for a few days and then gradually increase activity. A 'sani-chair' which can be wheeled over an ordinary lavatory outside the ward is usually preferable to the bedpan. In severe cases, or when there have been complications, restriction to bed for longer periods is necessary and also a longer time should be spent convalescing in hospital. Nowadays severe restrictions are no longer imposed on those who feel well and most patients can leave hospital in less than three weeks. Thereafter a few weeks of progressive rehabilitation should be supervised by the practitioner and most patients are fit to return to their previous occupation, or a more suitable one, within two to three months from the onset of the acute attack.

ANTICOAGULANTS. There is still a considerable difference of opinion as to the value of anticoagulant drugs in the treatment of acute myocardial infarction apart from their use in the prevention of thromboembolic complications on the venous side of the circulation. There is a general trend now to reserve them for relatively severe cases and to give them for a shorter period of time, e.g. three weeks, until the patient is fully ambulant. Long-term anticoagulant treatment for 3 to 6 months is indicated in the relatively young with a history of recurrent infarction if the patient is co-operative and reliable laboratory control is available. Oral anticoagulants, such as warfarin and phenindione, are not fully effective for 24 hours and require facilities for estimation of the prothrombin ratio to control dosage. The details of anticoagulant therapy are discussed on page 309.

CORONARY CARE UNITS. These units have been established in many hospitals for supervising patients with suspected acute myocardial infarction. Their aim is to detect and correct arrhythmias in order to prevent cardiac arrest, shock and cardiac failure. They require specially trained staff and equipment so that resuscitation, defibrillation and pacemaking can be undertaken immediately. The ECG of each patient is monitored so that it can be seen on an oscilloscope and activate an alarm if the heart rate increases or falls beyond set levels. Most patients are free of complications by the third day and can then be transferred to a ward for less intensive care.

Prognosis. Sudden death is the first manifestation of coronary heart disease in about 25 per cent of cases. About 60 per cent of those who die from acute myocardial infarction do so before medical help can be called. After the first 48 hours mortality decreases rapidly. Following recovery from an acute attack, some 10 per cent will die within a year, 30 per cent within five years and 60 per cent within 10 years. Mortality increases with age, a past history of myocardial infarction, prolonged pain, cardiac failure, shock, arrhythmias or embolism. Other adverse signs include triple rhythm and defects of conduction. Long-term survival is probably more likely if the patient accepts advice in regard to giving up smoking cigarettes, reducing obesity and taking regular exercise.

Prevention of Ischaemic Heart Disease

Coronary patients, that is to say those with symptomatic disease and the coronary prone, namely those with a number of high-risk factors, should be advised to modify their habits in the direction of healthier living. These individuals should be advised about stopping cigarette smoking for life and about weight control. Abnormalities such as hypertension, hyperlipidaemia and diabetes must be corrected. Women at risk for other reasons should not use the contraceptive pill. Advice about regular exercise, diet and emotional stress is particularly important.

Exercise. A distinction should be made between energy expenditure and the improvement of cardiopulmonary function. Every form of muscular contraction uses calories and regular daily exercise promotes loss of weight in the obese. However, exercise tolerance improves only if physical activity is sufficiently vigorous to cause tachycardia and dyspnoea. This is very beneficial even when carried out for only short periods.

Patients who have made a good recovery from myocardial infarction improve further, and safely, if exercise is begun gently and gradually increased under medical supervision. Pain, undue dyspnoea and fatigue must, of course, be avoided.

Diet. Obesity must be corrected by the methods described on page 177. Although as yet there is no proof that reduction of serum lipids prevents coronary disease, it seems reasonable to reduce lipid levels in the high risk individual. There seems little point in doing so in the patient with advanced coronary disease or in the elderly. The intake of saturated fats should be reduced but may be substituted by polyunsaturated fats. This means a decrease in the consumption of visible fat, especially in the form of butcher's meat and dairy products and invisible fat in the form of such foods as cakes, pastries, thick soups, sauces, mayonnaise and most cheeses except the cottage variety. Butter and hard margarine must be avoided and soft margarines used instead. Eggs are rich in cholesterol and should be restricted. Fruit, vegetables and salad can be taken in abundance. Attention to these principles will suffice in most cases. A special diet (Diet no. 10, p. 1000) and, if necessary, drugs such as clofibrate are required in resistant cases and in certain of the familial hyperlipidaemias with which atherosclerosis, diabetes and obesity are associated. The rational selection of diet and drug therapy is facilitated by knowledge of the plasma lipids but these should not be assessed until 6 weeks after a myocardial infarct as temporary changes occur immediately after the acute incident. If high serum lipid levels persist in spite of dietetic adjustments, clofibrate is indicated in a dose of 2 g daily unless the abnormality is due to a rise in the beta lipoproteins, in which case cholestyramine is the drug of choice. The triglyceride level is increased by obesity and by the consumption of alcohol; the therapeutic implications are obvious.

Stress. Reduction in emotional tension is important for coronary patients and the coronary prone; this can frequently be achieved if the doctor will spend sufficient time and patience on giving appropriate advice tailored to the individual's requirements. Although a tranquilliser or an adrenergic antagonist may help the anxious patient with angina, the real need is for more sensible living as those concerned almost always realise.

HYPERTENSION

Although in most cases of hypertension the cause is obscure some cases are secondary to recognisable disease. For this reason before starting treatment each patient should be investigated to ascertain whether any remediable underlying condition is present.

CAUSES OF SECONDARY HYPERTENSION

RENAL DISORDERS

(*a*) Acute proliferative glomerulonephritis.
(*b*) Chronic glomerulonephritis.

(*c*) Chronic pyelonephritis.
(*d*) Polycystic disease.
(*e*) Renal disease associated with renal ischaemia.

ENDOCRINE DISORDERS

(*a*) Phaeochromocytoma.
(*b*) Cushing's syndrome.
(*c*) Primary aldosteronism (Conn's syndrome).

COARCTATION OF THE AORTA (p. 292).

PREGNANCY. Hypertension in pregnancy may be due to coincidental essential hypertension, to pre-existing renal disease or to pre-eclamptic or eclamptic toxaemia.

Essential (Idiopathic) Hypertension

Aetiology. Essential hypertension is the name given to the type for which no cause can be found. The diagnosis is accordingly made by a process of exclusion. It is by far the most common form and affects the sexes about equally. The main incidence falls between the ages of 40 and 60 years and it is often a serious condition.

Heredity is important. It has been estimated that if both parents have hypertension the incidence of the disease in the children is about 45 per cent and if one parent has hypertension about 30 per cent. If the patient is under 35 years and there is no family history of hypertension, an underlying cause is likely to be present.

The part played by temperament and emotional factors is difficult to assess. Many authorities consider that hypertensives have exceptionally labile vascular systems and react to nervous stimuli by rises in blood pressure, but the evidence for a specific personality type is not convincing.

Pathogenesis. In most cases of hypertension the high blood pressure must be secondary to increased peripheral resistance because the other two factors which determine the height of the blood pressure, i.e. cardiac output and the viscosity of the blood, are unchanged.

It has been shown that this increased resistance occurs chiefly in the arterioles and is more severe in the renal vessels than elsewhere. Except in advanced cases the blood pressure is labile, and any measure which reduces sympathetic tone and causes vasodilatation will result in a substantial fall of blood pressure. It follows that the hypertension must at first be due to vasoconstriction rather than to narrowing of the vessels from organic disease; this might be due to neurogenic stimuli, i.e. increased sympathetic tone, or to humoral stimuli, i.e. a circulating pressor substance acting directly on the arterioles.

In animals it has been shown that the experimental production of renal ischaemia by partial occlusion of one renal artery results in hypertension which is independent of the nerve supply to the kidneys and is due to the liberation into the circulation of renin formed in the damaged kidney. No humoral hypertensive substance has been isolated in patients with essential hypertension.

Chronic renal disease of all types is often associated with hypertension, and it may be that in this group the mechanism is similar to that of experimental renal hypertension, i.e. reduced renal blood flow. Moreover, in cases of unilateral renal disease removal of the affected kidney or restoration of the lumen of an occluded renal artery will sometimes lead to cure of the hypertension. In human essential hypertension the haemodynamic effects and the pathological changes are essentially the same as in experimental renal hypertension, but it is still undecided whether the kidney is primarily or secondarily involved. It has been shown that, while in young people hypertension may be manifest before any structural changes can be demonstrated in the arterioles, in older subjects it is almost invariably accompanied by arteriosclerosis. This progression suggests that the changes are secondary to the hypertension rather than the reverse. A vicious circle may be set up whereby vascular narrowing leads to hypertension and hypertension to further vascular narrowing.

Pathology. The small arteries and arterioles are particularly affected. In the initial stage, hypertrophy of the media, splitting of the internal elastic lamina and collagenous thickening of the intima occur. Later, degenerative changes develop with atrophy of muscle fibres and overgrowth of connective tissue with subsequent hyalinisation. Swelling of the intima leads to progressive narrowing of the lumen. These changes are often referred to as '*arteriolar sclerosis*', and are particularly well seen in the kidneys of patients with essential hypertension. They are also found in the vessels of the pancreas, spleen and liver. Since the pathological changes in the kidney are patchy in distribution patients with arteriolar sclerosis seldom die from renal failure but succumb to cardiac failure or a cerebral vascular accident.

If hypertension develops rapidly in a severe form, as occurs in patients with malignant hypertension, still more extensive damage to the arterioles may result. These changes include necrosis of the vessel wall, which is infiltrated with a fibrin-like material, and the intima may be markedly thickened. Hence the term '*arteriolar necrosis*'.

Clinical Features. High blood pressure is often found on routine examination, e.g. for life insurance. Usually there are no symptoms for many years although they may develop due to worry about having high blood pressure. Unfortunately, the doctor is often responsible for sowing the seeds of anxiety. Early symptoms which are frequently attributed to hypertension are difficult to differentiate from those associated with psychological factors, e.g. headache, dizziness, nervousness, irritability, loss of energy, easy fatigue and insomnia.

In the early stage there are usually no abnormal physical signs other than the hypertension which initially is intermittent. The blood pressure is unusually labile, rising to an abnormal degree under the influence of such stimuli as emotion, exercise and cold. Later the resting blood pressure becomes permanently elevated.

The precise level of the blood pressure is not necessarily the most important criterion of severity of the disease. More valuable information will be obtained by examining the optic fundi and the heart and assessing renal function. In cases of similar severity as judged by the height of the blood pressure the disease may run very different courses. In some the condition is remarkably benign. Only in the late stages is there evidence of impaired renal function, and most patients nowadays die from the effects of atherosclerosis in heart or brain while still maintaining adequate renal function.

Complications. HYPERTENSIVE HEART DISEASE. At first the left ventricle maintains a normal blood flow to the tissues by increasing its force of contraction. This is achieved by dilatation of the heart and subsequent hypertrophy of the muscle fibres. Later, left ventricular output can no longer be maintained and signs of cardiac failure become manifest. Coronary artery disease is frequently associated with hypertension and aggravates the position.

The aortic component of the second heart sound may be accentuated. Enlargement of the heart may be recognised by outward displacement of the apex beat with a heaving impulse. Radiological examination confirms the cardiomegaly and electrocardiography shows evidence of left ventricular hypertrophy (Fig. 29, p. 219).

Later, breathlessness and attacks of paroxysmal dyspnoea may develop. Regular sinus rhythm is usually maintained but atrial fibrillation sometimes occurs. Triple heart rhythm and pulsus alternans are both signs of serious cardiac involvement. With the establishment of left ventricular failure crepitations are audible at the bases of the lungs and there are radiological signs of pulmonary oedema. Finally all the signs of right ventricular failure appear.

CEREBRAL MANIFESTATIONS. Minor symptoms include headache, dizziness and vertigo. These may be present in some cases but are more often due to cerebrovascular disease than to the hypertension. Later the defective blood supply may cause emotional lability and deterioration in mental powers. Major disturbances are hypertensive encephalopathy, cerebral haemorrhage and cerebral thrombosis.

Hypertensive Encephalopathy. This uncommon condition is due to acute focal cerebral ischaemia in which cerebrovascular spasm, oedema or minor degrees of haemorrhage or thrombosis play a part. Transient disturbances of vision or speech, pareses, paraesthesiae, disorientation and fits or loss of consciousness may occur. The blood pressure and often the cerebrospinal fluid pressure rise considerably during the attack. Recovery usually takes place and there is no permanent loss of function.

Cerebral Thrombosis (p. 844) *and Cerebral Haemorrhage* (p. 846) commonly occur.

THE EYE IN HYPERTENSION. Vascular lesions secondary to hypertension may be responsible for haziness of vision, progressive deterioration or sudden loss of vision, visual field defects or diplopia. The state of the ocular fundus (Plate I) is a better guide to prognosis than the height of the blood pressure.

Arteriosclerotic changes are usually best seen after the third branching of the central retinal artery. As the wall of the vessel thickens, the colour of the blood column becomes paler and its width decreased. These changes are accompanied by broadening of the light reflex, irregular variations in calibre and later there may be white sheathing on either side of the artery. These changes are commonly accompanied by deflection of the veins at arteriovenous crossings, and where compression is present, banking of the distal blood column will be seen.

Haemorrhages of all kinds may occur, but most are superficial in the nerve fibre layer and are therefore linear or flame shaped in form. They fade without trace in a few weeks at the most.

Hard exudates are small, dense whitish deposits lying deeply and consisting of lipid. They remain relatively unchanged for months or years.

Soft exudates ('cotton wool spots') lie superficially among the retinal vessels and are recognised by their white fluffy appearance. They are areas of retinal infarction or ischaemia and are indicative of occlusion of very small arterioles. In the context of a raised blood pressure they are indicative of the early stages of malignant hypertension. They fade and leave no visible trace in a few weeks or less.

Papilloedema in the presence of the other changes of hypertensive retinopathy indicates a more advanced stage of malignant hypertension; the patient is likely to die from renal failure within months due to acute fibrinoid necrosis of afferent arterioles to the glomeruli unless prompt action is taken to lower the arterial pressure.

The presence of soft exudates or papilloedema is indicative of a very poor prognosis if treatment with antihypertensive drugs is not urgently instituted.

RENAL MANIFESTATIONS OF HYPERTENSION. The possible role of the kidney in the pathogenesis of hypertension has already been discussed. Renal arteriosclerosis is progressive as hypertension advances but impairment of renal excretory function occurs late or not at all in benign essential hypertension. In malignant hypertension arteriolar necrosis usually occurs in the renal vessels and consequently impairment of renal function is usually rapid and progressive; death frequently occurs from uraemia. Proteinuria rarely exceeds 2 g/day. Larger amounts, or the finding of granular casts or red cells, suggest the presence of chronic nephritis or malignant hypertension.

Polyuria by day is usually a sign of tubular dysfunction, but nocturia may be secondary to the reabsorption of oedema fluid which tends to occur in the recumbent posture. Renal function is rarely improved by treatment of hypertension.

MALIGNANT HYPERTENSION. Essential hypertension may be divided into benign and malignant groups, the diagnostic criterion of the second group being the presence of papilloedema. Papilloedema may occur after many years of known benign essential hypertension or develop rapidly in one whose blood pressure was known previously to have been normal, the whole course of the disease taking less than two years. Papilloedema may complicate chronic nephritis or develop during an attack of hypertensive encephalopathy or occur in cases of transient hypertension such as acute nephritis or toxaemia of pregnancy. It is not therefore a satisfactory criterion by itself on which to differentiate the various forms of hypertension.

It has been disputed whether malignant hypertension is a separate condition or merely a terminal phase of benign hypertension. From the pathological point of view it has been suggested that its development can be explained on the severity and rapidity of onset of the arteriolar lesions, and the essential difference is that between arteriolosclerosis and arteriolonecrosis (p. 275). It has been postulated that a vicious circle develops.

If the term malignant hypertension is to be used it should be confined to the clinical syndrome of severe diastolic hypertension with papilloedema and renal failure which occurs mainly in males in the third and fourth decades and which pursues a rapidly downhill course to death from uraemia within a year unless suitable treatment is instituted. Most cases of malignant hypertension before the age of 30 are caused by chronic pyelonephritis or glomerulonephritis. When papilloedema and renal failure develop in a person known to have essential hypertension this disease is sometimes described as having entered the 'malignant phase' or as 'accelerated hypertension'.

Treatment of Essential Hypertension

The management of the patient rather than the disease must be emphasised. Psychological factors are important; the family doctor can do much to help his patient deal with unnecessary stress and worry. Concern over the height of the blood pressure need no longer be a source of anxiety if due explanation is given with reassurance that, with modern treatment, the outlook has greatly improved and almost always a normal or near normal life can be continued.

There is no specific treatment because no specific cause for essential hypertension has been found. The aim of therapy is to lower the blood pressure without undue side-effects and this can almost always be achieved.

Strong indications for immediate treatment include left ventricular failure, progressive left ventricular hypertrophy, hypertensive encephalopathy and retinopathy. Moderately strong indications include a cerebrovascular accident or angina pectoris, but caution is required when there is much evidence of associated atherosclerosis. In such cases the blood pressure should be lowered gradually and only to a moderate degree and postural hypotension avoided: otherwise complications such as myocardial infarction, aggravation of mental changes or cerebral infarction may occur. The presence of considerable renal failure (blood urea greater than 100 mg/100 ml) is a contraindication to the use of potent anti-hypertensive drugs.

It has now been clearly shown in prospective studies that even mild hypertension of the order of 165/95 is potentially dangerous, particularly in males and that early treatment will protect against hypertensive strokes and cardiac and renal failure. In borderline cases treatment should always be advised if there is a family history of hypertension.

General Measures. In all cases advice should be given on healthy living in relationship to diet, smoking, physical exercise and avoidable emotional stress (p. 272). The patient should be kept under review.

Rest. In the early stages rest in bed is unnecessary but slight restrictions may be advisable such as going to bed early and resting after meals and perhaps also at the weekends. It is important to cultivate the art of relaxation. When cardiac failure is manifest, rest in bed is indicated until the failure is controlled by treatment.

Physical Activity. There is no evidence that moderate exertion is harmful and walking or playing golf, within the limits of dyspnoea or undue tiredness, is to be encouraged. Strenuous occupations, sudden stress and prolonged exertion are to be avoided. Overwork, worry and emotional stress are just as harmful as physical over-exertion.

Diet. Reduction of weight is important in obese persons. The avoidance of salty foods and added salt is advisable and may permit a reduction in the dose of antihypertensive drugs. A low salt diet, i.e. less than 1 g sodium per day (Diet no. 8, p. 998) will often result in a significant reduction of the blood pressure but is so irksome that patients can rarely be persuaded to take it for more than a few weeks. Hence it is not recommended for the treatment of hypertension unless all other measures have failed.

As atherosclerosis is frequently associated with hypertension, the dietetic advice as given to the coronary prone (p. 273) is also applicable.

Anti-hypertensive Drugs. A number of drugs are now available which have the effect of lowering the blood pressure by reducing the cardiac output or the peripheral vascular resistance. In the more severe cases the dosage is best stabilised in a hospital where there are adequate facilities for close observation and control. Individual requirements vary widely and in general it is best to start with a small dose and gradually increase it until the blood pressure is controlled without undue side-effects. Some drugs are best used in combination.

SYMPATHETIC BLOCKING DRUGS. These preparations have a selective action on the post-ganglionic sympathetic nerves.

Debrisoquine should be administered initially in a small dose of not more than 10 mg twice daily and gradually increased at three-day intervals—first to 10 mg thrice daily and then by increments of 10 mg per day until the standing diastolic blood pressure is as near normal as possible without postural symptoms or side-effects. If necessary, the drug may be given in combination with an oral diuretic or some other antihypertensive preparation.

Bethanidine has a similar pharmacological effect in blocking the transmission of sympathetic impulses but is more quickly absorbed and excreted. This is sometimes an advantage, but is somewhat more likely to result in postural hypotension. Dosage is similar to that of debrisoquine.

Guanethidine is excreted relatively slowly and therefore, after an initial dose of 10 mg twice daily, increments should be more gradual. Side-effects include diarrhoea, muscular weakness, nasal stuffiness, frequency of micturition and sexual difficulties in the male, but these can usually be reduced in frequency and severity if dosage is carefully adjusted to each patient's requirements.

Methyldopa has a somewhat different mode of action in that it results in the substitution of a relatively weak transmitter (alpha-methyl noradrenaline) at the nerve endings. Almost all patients feel drowsy for the first 48 hours on treatment; thereafter side-effects are usually mild, e.g. dryness of the mouth and sedation. More serious toxic effects are haemolytic anaemia (p. 38), fever and jaundice. Treatment should be commenced with 250 mg thrice daily and the dose increased by 250 mg each day until the desired effect is achieved, or a maximum of 3 g daily is reached.

Clonidine is a potent antihypertensive agent with actions and side-effects similar to methyldopa with the exception of haemolytic anaemia. The daily dose is 0·3-1 mg. It does not produce postural hypotension but excessive sedation is quite common.

ADRENERGIC BETA-RECEPTOR ANTAGONISTS. Beta-receptor blockade can now be achieved with propranolol and similar preparations (p. 235). Propranolol may be used as the sole antihypertensive agent, but dosage may have to be very high (up to 1-3 g per day) and in consequence it is more often used in combination with other antihypertensive drugs. Blood pressure reduction is achieved by decrease in heart rate and in cardiac output and there is no postural hypotension. Propranolol is also of value in the treatment of angina, to which many patients with hypertension are prone on account of associated atherosclerosis.

DIAZOXIDE. This drug which is related to the thiadiazines (p. 195) is a potent hypotensive agent when given rapidly in a dose of 300 mg i.v. It is valuable in the management of acute hypertensive crises but tends to produce hyperglycaemia with repeated use.

DIURETICS. Oral diuretics have themselves a mild antihypertensive effect but their principal use in the management of hypertension is as an adjuvant when the blood pressure is difficult to control with sympathetic blocking drugs, either because of resistance or the incidence of side-effects. A small dose of chlorthalidone (50 mg) or polythiazide (2 mg) daily is often sufficient.

RAUWOLFIA. Rauwolfia and its derivatives (e.g. reserpine) have a mildly hypotensive action and are also sedative. The effects develop slowly over several days and not all patients respond. There are many side-effects, e.g. nasal congestion, lethargy, unpleasant dreams and diarrhoea. The only serious one which is at all common is depression, often with agitation and occasionally with suicidal tendencies. It is most important to be on the alert for this complication and stop the drug. The recommended dose of reserpine is 0·25 mg once or twice daily. It is sometimes used in combination with other agents, particularly diuretics which potentiate its antihypertensive effect. In Britain it is now little used because more effective drugs are available.

CHOICE OF DRUG THERAPY. In the mild case a diuretic with or without a tranquilliser may be sufficient. In cases of moderate severity methyldopa may be used but it is ineffective or poorly tolerated in about half the patients. Debrisoquine is most suitable for severe hypertension. Often control is more satisfactory if a diuretic or a beta blocking drug is added; the latter is indicated especially if there is angina, tachycardia or emotional lability. Bethanidine is useful because of its rapid absorption if the physician wishes to control the blood pressure promptly but if there is not sufficient urgency to warrant giving

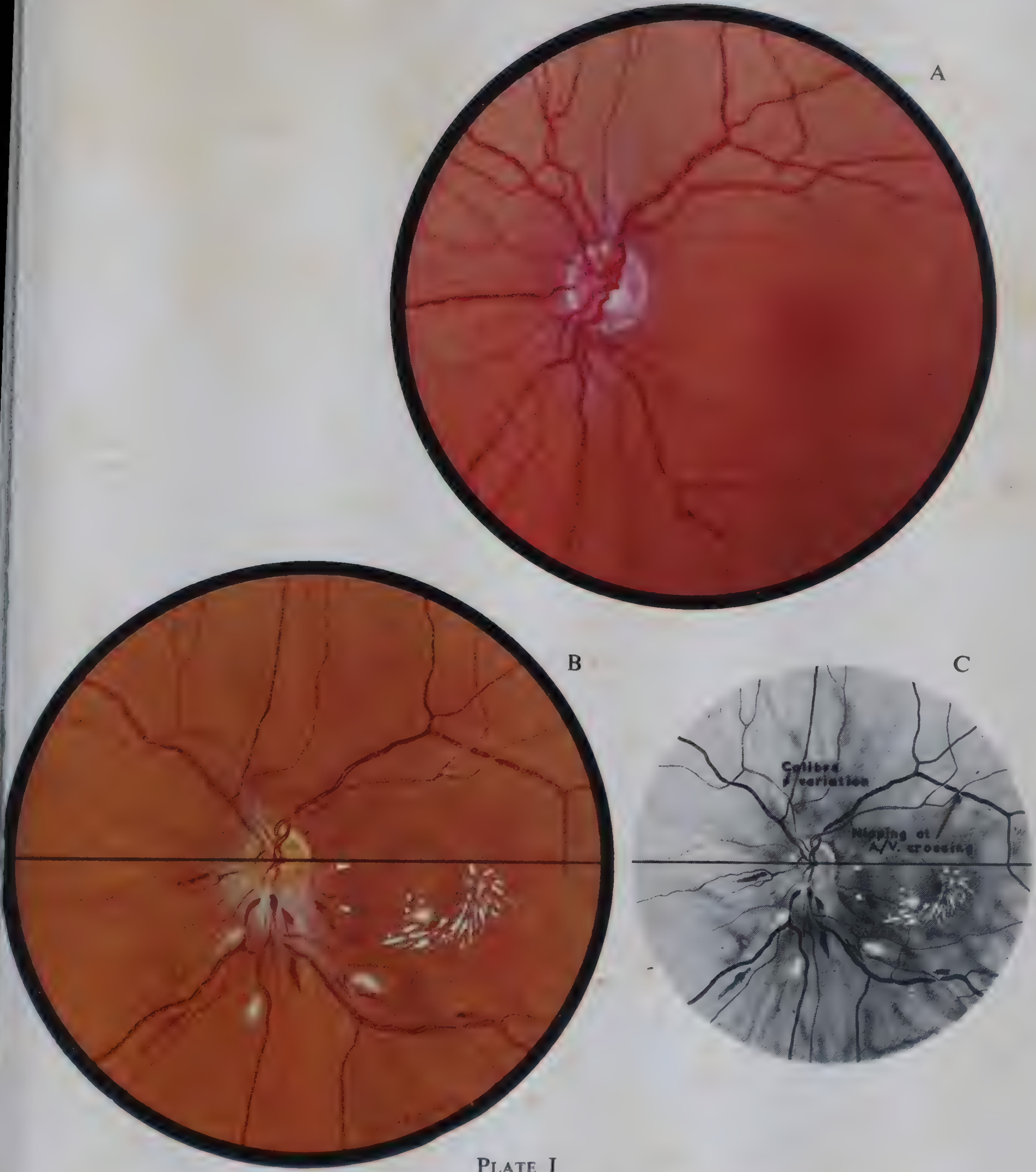


PLATE I

A, Normal retinal vessels. B, Hypertensive retinopathy. The upper half of this painting shows the retinal blood vessels in hypertension of moderate severity. The arteriolar blood column is narrower than normal and a central white streak ('reflex') is visible or is more prominent than normal. Irregularity of breadth of the arteriolar blood column indicates an irregular lumen. Veins at arterial-venous crossings are narrowed ('nipping'), partly because of pressure by arterioles and also because opacity of the arterial wall obscures the venous blood column. The lower half of the painting shows severe hypertensive retinopathy. Haemorrhages and 'soft' exudates are added to the abnormalities seen in the upper half and these are also more marked. C, Key to B.

(By permission of Professor C. I. Phillips, Department of Ophthalmology, University of Edinburgh)

a drug by injection. In an emergency, for example in pulmonary oedema or encephalopathy with a very high blood pressure, diazoxide may be used or debrisoquine or bethanidine given parenterally.

Prognosis of Hypertension

Insurance statistics show that, in general, expectation of life is considerably reduced in those who have high blood pressure compared with those in whom the pressure is within the normal range. However, it does not follow that *all* who have high blood pressure necessarily have a bad prognosis. Many live a life of normal span free from relevant illness. Included in this category are individuals who have labile blood pressures with hypertension due to emotional causes and others in whom casual readings are raised but who have normal pressures at rest. On the whole, women appear to withstand hypertension better than men. Many middle-aged women in whom pressures whenever recorded are of the order of 220/120 but who have no relevant symptoms and no changes in fundi or heart, remain in good health for many years.

Other individuals, particularly relatively young men, who when first seen have high diastolic pressures together with secondary manifestations in the fundi or heart, undoubtedly require optimal control of the blood pressure without delay.

Consideration of the family history, the age of the patient and an estimation of the rate of progression of the various manifestations will give the data on which to judge the probable course of the disease. The condition is mild if the heart is not enlarged, the fundi show no abnormalities and there is no proteinuria or evidence of impaired renal function. On the other hand patients with untreated malignant hypertension rarely live for more than a year.

When properly administered to a suitable patient modern treatment is effective in relieving symptoms, preventing or postponing complications and in prolonging life, but treatment of hypertension continues to be difficult and necessitates much attention to detail and considerable patience on the part of both patient and doctor. There is, as yet, no entirely satisfactory preparation for lowering the blood pressure; that is to say one which does not produce in some patients tolerance, undesirable side-effects or occasional unpredictable hypotension. In addition, it should be remembered that, once begun, treatment will probably have to be continued for life. It is therefore evident that most careful consideration should be given to the issues discussed above before making the decision to administer antihypertensive drugs.

PULMONARY FACTORS IN HEART DISEASE

Pulmonary Arterial Hypertension

An increase of pressure in the pulmonary arterial circulation may occur:

(1) secondary to a passive rise of pressure in the left atrium and hence in the pulmonary veins in mitral stenosis or in left ventricular failure;

(2) as a result of diminution in the pulmonary capillary bed and hypoxic pulmonary vasoconstriction in emphysema;

(3) as a result of obstruction to the pulmonary circulation, e.g. from arterial narrowing or recurrent emboli;

(4) from increased pulmonary blood flow in association with some forms of congenital heart disease;

(5) rarely, without obvious cause (idiopathic or primary pulmonary hypertension).

Pulmonary hypertension may be inferred if there is accentuation of the pulmonary second sound, enlargement of the pulmonary artery and right ventricular hypertrophy. In some cases it is necessary to prove the existence or otherwise of pulmonary hypertension by cardiac catheterisation before deciding on the surgical treatment of heart disease.

Pulmonary Embolism and Infarction

Pulmonary embolism occurs when a portion of thrombus in a systemic vein, or, less commonly, in the right side of the heart is discharged into the circulation. It may lodge in the pulmonary trunk and cause sudden death, or in a smaller pulmonary artery and result in pulmonary infarction. Pulmonary embolism is the commonest cause of acute respiratory illness in hospital patients in the western world.

Aetiology. Thrombosis in the deep veins of the legs (p. 307) is the most frequent source of pulmonary embolism. As this is usually the result of stasis, embolism most often affects people who have been confined to bed. It is particularly liable to occur within ten days after a surgical operation or after childbirth. The presence of phlebothrombosis is frequently not recognised until after the embolism.

In less than 10 per cent of cases, thrombi responsible for pulmonary embolism form in the right atrium in patients with atrial fibrillation, especially if cardiac failure is present.

Clinical Features

PULMONARY EMBOLISM. With massive pulmonary embolism the patient may suddenly be seized with a sensation of great oppression in the chest and intense dyspnoea followed by cyanosis and shock. Death may occur within a few minutes, an hour or two or a day or two. Recovery is the rule if the patient survives the first few hours, but there is at least a 25 per cent risk of recurrence. Pain indistinguishable from that of myocardial infarction may occur due to a combination of decreased coronary blood flow and hypoxaemia. The blood pressure falls, the jugular venous pressure rises and cardiac failure may follow in severe cases. The pulmonary second sound may be accentuated and triple rhythm may develop. These signs are due to a combination of right ventricular failure and a low cardiac output.

In cases of lesser severity symptoms and signs may be absent or there may be transient dyspnoea, tachycardia or syncope. Recurrent embolism may result in pulmonary hypertension which may be followed by right ventricular failure.

PULMONARY INFARCTION. The onset is sudden with either pleuritic pain or haemoptysis as the initial symptom. These two symptoms are not always present and the absence of one or even both of them does not necessarily exclude pulmonary infarction. The pain is often severe and the haemoptysis may be repeated. Other clinical features include tachycardia, dyspnoea and cyanosis. Pyrexia is usually present; in the early stages it is probably due to absorption of blood from the infarct, but later it may be due to secondary infection. A polymorphonuclear leucocytosis may be present, even in the absence of infection.

Radiological Examination. In *massive pulmonary embolism* the lung fields often appear normal but sometimes there is a hilar opacity from the blocked vessel and ischaemia distal to the embolus causes a reduction in the normal vascular markings of a lung or lobe.

In *pulmonary infarction* there may be a pulmonary opacity or a linear scar representing the infarct. A small pleural effusion is common. One hemidiaphragm may be raised or paralysed. These radiological abnormalities are usually most marked at the base of one lung but are often bilateral.

Venous thrombosis is demonstrated by bilateral ascending or femoral phlebography (p. 308).

RADIO-ISOTOPE STUDIES. These procedures may reveal the presence of ischaemic areas not detected on the plain radiograph of the chest; serial studies are helpful in monitoring progress.

Electrocardiography. In cases of massive embolism the ECG may show a diagnostic pattern, namely right axis deviation and inversion of T waves in the right ventricular leads, or the pattern of right bundle branch block. The ECG is usually normal in cases of lesser severity.

Differential Diagnosis. Pulmonary embolism and infarction are very frequently misdiagnosed.

1. Massive pulmonary embolism must be distinguished from myocardial infarction by the characteristic ECG and enzyme changes in the latter.
2. Pulmonary infarction must be distinguished from:
   (i) Dry pleurisy of infective origin, by the character of the sputum and the response to antibiotics.
   (ii) Spontaneous pneumothorax, by the characteristic physical and radiological signs.
   (iii) Other causes of haemoptysis, e.g. tuberculosis, mitral stenosis, neoplasm, bronchiectasis.

Course and Prognosis. Massive pulmonary embolism is frequently fatal. Minor- and medium-sized emboli are much less dangerous unless they are followed by further embolisation which may itself be fatal. In retrospect it is often apparent that small 'herald' emboli have, in fact, been missed or misinterpreted. Recurrent emboli may cause chronic pulmonary hypertension and right ventricular failure. The vast majority of pulmonary infarcts resolve completely. Occasionally an infarct may become secondarily infected and result in lung abscess or empyema.

Prophylaxis. The prevention of venous thrombosis is very important and is discussed on page 309. An appreciation of the potential dangers of bed rest, together with the use of anticoagulants once venous thrombosis has occurred, are the principal factors in the prevention of pulmonary embolism and infarction.

Treatment. Pain and apprehension must be allayed. Oxygen should be administered if cyanosis is present. Anticoagulants (p. 309) should be given in order to prevent further venous thrombosis in the legs. Thrombolytic drugs, such as urokinase, accelerate recovery from pulmonary embolism and are under trial; they are very expensive and their control is difficult.

Management of massive pulmonary embolism is best conducted in an area where intensive care can be provided. Occasionally a large embolus may be successfully removed from the main pulmonary artery. The chances of survival are greatest if embolectomy is carried out with the aid of cardiopulmonary bypass. In cases of recurrent pulmonary embolism despite anticoagulation venous interruption may be necessary either by ligating the femoral vein or plicating the inferior vena cava depending on the source of the embolus.

Pulmonary Heart Disease secondary to Chronic Bronchitis and Emphysema

The term 'pulmonary heart disease' or 'cor pulmonale' means right-sided heart failure secondary to disease of the lungs or pulmonary vessels. In industrial regions of England chronic respiratory disease is the most common cause of cardiac failure. Less frequently right ventricular failure results from pulmonary fibrosis (p. 408) or from recurrent pulmonary emboli.

Pathogenesis. Impaired alveolar ventilation, structural abnormalities of the pulmonary vasculature and defective aeration of the blood lead to hypoxia which is responsible for polycythaemia and hypervolaemia. There is evidence that hypoxia itself leads to reflex pulmonary hypertension. In addition there may be carbon dioxide retention (hypercapnia).

Clinical Features. The symptoms and signs are those of the underlying pulmonary disease together with those of right-sided heart failure. The onset is usually insidious but may apparently come on suddenly following an acute respiratory infection.

Sinus rhythm is the rule and if there is atrial fibrillation co-existing coronary disease should be suspected.

The earliest radiographic sign is enlargement of the pulmonary artery and its two main branches followed by enlargement of the right ventricle. If severe pulmonary hypertension is present electrocardiograms will show the pattern of right ventricular hypertrophy.

Diagnosis. One should suspect that there is underlying lung disease when right-sided heart failure cannot be explained by left-sided heart disease. The diagnosis can be confirmed by pulmonary function tests (p. 328). The most valuable of these is the carbon dioxide tension as this is nearly always raised in pulmonary heart disease and usually subnormal in heart failure of other types.

Treatment

(*a*) Prompt and thorough treatment of any pulmonary infection is frequently the most efficacious factor in treating the cardiac failure.

(*b*) Oxygen is indicated if central cyanosis is present but caution is necessary because cerebral symptoms and even coma can result from carbon dioxide retention if the concentration of oxygen is not kept below 30 per cent.

(*c*) Diuretics should be given as with all forms of cardiac failure; digitalis may also be required but is relatively ineffective.

(*d*) Sedatives must be used with great caution owing to their action in depressing the respiratory centre.

(*e*) Airway obstruction is treated with bronchodilators, physiotherapy, etc. as described on page 389.

The results of treatment are often disappointing and a recurrence of cardiac failure is seldom long delayed.

DISEASES OF THE MYOCARDIUM

The myocardium is involved in most types of heart disease, but the terms myocarditis and cardiomyopathy are usually applied to those relatively uncommon forms of myocardial disease which are not the result of rheumatic fever, coronary artery disease or hypertension.

Acute Myocarditis

Aetiology. Acute myocarditis usually occurs as a complication of infections, the majority being due to the toxic effects of diphtheria, pneumonia, typhoid fever, scrub typhus fever and meningitis; it also occurs in protozoal infections such as Chagas' disease (American trypanosomiasis, p. 974) and may follow virus diseases such as influenza, poliomyelitis, infectious mononucleosis and, particularly, Coxsackie-B infections.

Clinical Features. Often the only evidence of myocarditis is a sinus tachycardia which is out of proportion to the severity of the infection. In more severe cases there may be a gallop rhythm, arrhythmias and conduction defects and acute circulatory failure.

Prognosis in most types of acute myocarditis is usually good, but it may cause death in diphtheria. In Chagas' disease, the patient usually recovers from the acute phase and after a latent period of ten or twenty years, a chronic cardiomyopathy develops which is eventually fatal.

Treatment. There is no specific therapy for acute myocarditis; the usual forms of treatment for cardiac failure and arrhythmias should be undertaken. Prolonged rest is sometimes necessary.

Chronic Cardiomyopathies

Aetiology. In a considerable number of cases, the myocardial disease is part of a generalised disorder and the cardiac involvement may be of major or minor degree. Such disorders include haemochromatosis, sarcoidosis, amyloidosis, the muscular dystrophies and connective tissue disorders such as systemic lupus erythematosus, scleroderma and polyarteritis.

In the remainder there is no generalised disorder and frequently no aetiological agent can be found, although in a proportion of such cases there is a family history. Cardiomyopathy may be associated with alcoholism and the late stages of pregnancy and the puerperium (peripartum cardiomyopathy).

Endocardial fibroelastosis is a disorder of infants in which a thick, fibrous layer is superimposed on the endocardium of the left ventricle and frequently involves myocardium and the mitral valve. There may be associated congenital cardiac lesions and the usual course is one of progressive heart failure.

Clinical Features. The cardiomyopathies most often present in one or other of two clinical patterns: (1) The most common is '*Congestive*' with cardiomegaly and valvular regurgitation, and progressive left- and, later, right-sided cardiac failure. (2) '*Hypertrophic*' is frequently associated with such severe thickening of the interventricular septum that obstruction to outflow from the left ventricle occurs. This produces a clinical picture simulating aortic stenosis (idiopathic hypertrophic sub-aortic stenosis). There is usually no identifiable cause for this type of case although a familial history is quite common.

Two rarer types of presentation are (3) a '*Restrictive*' type simulating constrictive pericarditis and (4) an '*Obliterative*' type as in endomyocardial fibrosis which is a disorder confined to the humid areas of the tropics. Fibrotic tissue and thrombus obliterate the cavities of the left and right ventricles and may lead to mitral and tricuspid regurgitation. The cause of this disorder is unknown but nutritional or infective factors may contribute.

Diagnosis. The diagnosis of cardiomyopathy should be considered only after other forms of heart disease have been excluded, i.e. rheumatic, hypertensive, ischaemic, thyrotoxic or congenital, or if there is a generalised disorder of the type that is known to be associated with a cardiomyopathy.

Treatment. Treatment remains unsatisfactory for the majority of cases for which the cause is not known, cannot be removed or for which no specific treatment is available. A well-balanced diet is indicated in those cases in which a nutritional deficiency may be of aetiological importance and the avoidance of alcohol is essential if alcoholism is thought to be a provoking factor. Corticosteroid therapy is sometimes of value for the treatment of cardiomyopathy due to sarcoidosis or associated with connective tissue disorders.

Cardiac failure must be treated along the usual lines. Surgical resection of the hypertrophied septum is sometimes beneficial in the hypertrophic obstructive type.

DISEASES OF THE PERICARDIUM

Pericarditis cannot be considered as a disease entity because there are many different causes and the clinical manifestations and prognosis largely depend on the underlying disease. Nevertheless certain symptoms and signs may occur whatever the aetiology and merit independent description. Chronic constrictive pericarditis will be discussed separately.

Acute Pericarditis

Aetiology

1. Rheumatic fever.
2. Viral infection.
3. Tuberculosis.
4. Acute myocardial infarction.
5. Post-myocardial infarction syndrome.
6. Pyogenic infection.
7. Uraemia.
8. Malignant disease.
9. Trauma.
10. Connective tissue disease.
11. Idiopathic.

Pathology. Pericarditis may be fibrinous, serous, haemorrhagic or purulent. In fibrinous pericarditis there is a fibrinous exudate on the surface which leads to varying degrees of adhesion formation and hence of obliteration of the pericardial cavity. In serous pericarditis there is in addition a serous exudate of anything from a few ml to 2 litres. The effusion is straw-coloured and often slightly turbid with a high protein content. A haemorrhagic effusion suggests a malignant origin. Purulent pericarditis is due to a pyogenic infection and the effusion is rarely large.

Clinical Features. Symptoms and signs of the underlying causative disease will often be present. The clinical features will largely depend on whether or not a pericardial effusion is present.

PAIN. Precordial pain, which is not invariably present, may be sharp or aching in character. It may be made worse by movements, inspiration and lying flat. It is often severe in pericarditis of viral origin but is relatively uncommon in other cases, e.g. in pericarditis secondary to uraemia, myocardial infarction or malignant disease.

A sensation of precordial oppression may be produced by a large pericardial effusion.

FRICTION. Pericardial friction is the characteristic and diagnostic sign of pericarditis. It consists of a superficial scraping, scratching sound, usually best heard to the left of the sternum, often localised to a small area of the precordium and synchronous with the heart's action. It varies from time to time and may be transient. It may be aggravated by inspiration presumably because the adjacent pleural surface is involved.

EFFUSION. Signs of pericardial effusion are difficult to detect until about 500 ml of fluid have accumulated. The area of cardiac dullness is increased especially to the left of the sternum. The heart sounds may become muffled.

CARDIAC TAMPONADE. This term refers to compression of the heart by a large or rapidly increasing effusion or by constrictive pericarditis which interferes with diastolic filling of the heart. As a result the stroke output of the heart is diminished, tachycardia occurs, the blood pressure falls, the venous pressure is increased, and the clinical picture of shock may develop. Pulsus paradoxus may occur (p. 209).

RADIOLOGY. With a large effusion obliteration of the normal contours of the heart, widening of the base and diminished pulsation of the borders may be seen. Serial films may show significant changes of size over a short period of time.

ELECTROCARDIOGRAPHY. Serial electrocardiograms may reveal a diagnostic pattern in the ST segment and the T waves (p. 223).

Treatment, Course and Prognosis. This is essentially that of the underlying disease.

PARACENTESIS. Paracentesis of a pericardial effusion is rarely required but may have to be carried out for diagnostic purposes or to relieve severe symptoms from tamponade. The procedure is not without danger from puncture of the heart or of a coronary vessel and should be done only when strictly necessary. The needle is best inserted into the pericardial sac in the subcostal angle through the costoxiphoid notch and directed upwards, backwards, and to the left. Surgical drainage will usually be necessary if pus is found.

Clinical Features in Relation to Aetiology

Rheumatic Pericarditis. This is invariably associated with rheumatic endocarditis and myocarditis (p. 260).

Viral Pericarditis. Viral pericarditis often follows an upper respiratory infection and in some cases Coxsackie virus can be isolated. Recovery usually occurs within a few weeks without after-effects but recurrences may follow and an occasional death has been reported. There is no specific treatment.

Tuberculous Pericarditis. Tuberculous pericarditis may be secondary to manifest pulmonary or mediastinal tuberculosis, but the primary source may not be detectable. The disease sometimes begins with an acute febrile illness but is more commonly insidious in onset with vague malaise and low-grade fever. The subsequent course is chronic. An effusion usually develops and the pericardium may become thick and unyielding so that the heart is compressed. Pleural effusions are often associated.

The diagnosis may be confirmed by aspiration of the fluid and direct examination or culture for tubercle bacilli. Antituberculous chemotherapy is prescribed (p. 366). Aspiration must be carried out as required to relieve symptoms. There is evidence that corticosteroids may prevent the development of constrictive pericarditis. In the inactive stage surgical relief may be necessary.

Myocardial Infarction. Myocardial infarction may be complicated by fibrinous pericarditis if the infarct extends to the epicardial surface. The prognosis is not affected and no special treatment is required.

Post-myocardial Infarction Syndrome. The pericardium and often the pleura may be involved in an autoimmune reaction a few weeks or even months after myocardial infarction. The condition responds to corticosteroids but may recur.

Pyogenic Pericarditis. Purulent pericarditis may be due to direct spread from an intrathoracic infection such as an empyema, to blood stream infection, e.g. from osteomyelitis or a penetrating injury. It is rare in Britain now. Treatment is by surgical drainage and chemotherapy.

Uraemic Pericarditis. This is a serious sign in renal failure and the diagnosis is often made on discovering a pericardial rub, pain being unusual.

Malignant Pericarditis. This most commonly arises from direct extension of a bronchial carcinoma. The effusion when present may be haemorrhagic.

Traumatic Pericarditis. This may result from injury by the steering wheel in car crashes and from wounds through the chest wall.

Connective Tissue Diseases. Pericarditis may occur occasionally in this group of diseases particularly in systemic lupus erythematosis.

Idiopathic Pericarditis. In some cases no cause can be found despite full investigation.

Chronic Constrictive Pericarditis

A slowly progressive fibrosis of the pericardium develops as the result of previous infection and constricts the movement of the heart, so that it cannot expand in diastole. The fibrous tissue is thick, dense and inelastic; calcification is common. The inflow of blood to the heart is impeded so that the cardiac output is diminished and the systemic venous pressure increased with resultant peripheral congestion. The heart is otherwise normal, though secondary atrophy of muscle fibres may occur.

The recognition of this condition is important because it is amenable to surgical treatment.

Aetiology. Many cases are due to tuberculosis, some to a pyogenic infection and in others the cause is obscure. Often there is no definite history of previous acute pericarditis. Rheumatic fever does not cause constrictive pericarditis.

Clinical Features. Symptoms depend on the degree of constriction. Unlike other types of heart disease, breathlessness is not a prominent symptom and is rarely present at rest because the lungs are often not congested. Raised jugular venous pressure is a notable feature. Enlargement of the liver and ascites occur relatively early compared with peripheral oedema. Concomitant pleural effusions are common in the tuberculous cases.

The apex beat is difficult to feel and a triple rhythm may be heard from the addition of a sound in early diastole, the pulse is rapid and of small volume, and there may be pulsus paradoxus (p. 209). An important feature in most cases is the absence of much enlargement of the heart. This contrasts with almost all forms of cardiac failure. Atrial fibrillation occurs in about 30 per cent of cases.

Radiology. Calcification of the pericardium is frequently seen, particularly in lateral or oblique views. Screening may show a small 'quiet' heart with diminished pulsation. Sometimes there is apparent enlargement because the pericardium is so thick. Pleural effusion may obscure the cardiac outline.

Treatment. Medical treatment can produce only slight or temporary improvement. The problem is a mechanical one and surgical resection of as much as possible of the pericardium is indicated. The operation may produce dramatic relief and considerable improvement is usual, but it may take several months for maximum benefit to be obtained.

CONGENITAL HEART DISEASE

The incidence of congenital abnormalities is about 6 per 1,000 births. In most cases the underlying cause of the abnormality is unknown, but some fetal defects are due to maternal infections in the early weeks of pregnancy, e.g. rubella. All degrees of severity occur. Many defects are not compatible with extra-uterine life, or only for a short time. Some are particularly important to recognise because they may be amenable to surgical treatment. Infective endocarditis is an important potential complication.

A precise clinical diagnosis may be impossible in infancy but can usually be made with modern methods of investigation. Symptoms may be absent altogether or consist principally of breathlessness and failure of development. Local signs vary with the anatomical lesion. Central cyanosis occurs only when venous blood enters the systemic circulation. The most common cause of this is a septal defect combined with a severe grade of pulmonary stenosis or pulmonary hypertension. Often the signs are characteristic, e.g. in patent ductus arteriosus or in ventricular septal defect, but sometimes diagnosis is very difficult and special investigations such as cardiac catheterisation and angiocardiography are required.

Only the relatively common disorders likely to be met with in practice and those which are of practical importance will be described.

Patent Ductus Arteriosus

During fetal life, before the lungs begin to function, most of the blood from the pulmonary artery passes through the ductus arteriosus which joins the aorta just below the origin of the left subclavian artery (Fig. 51).

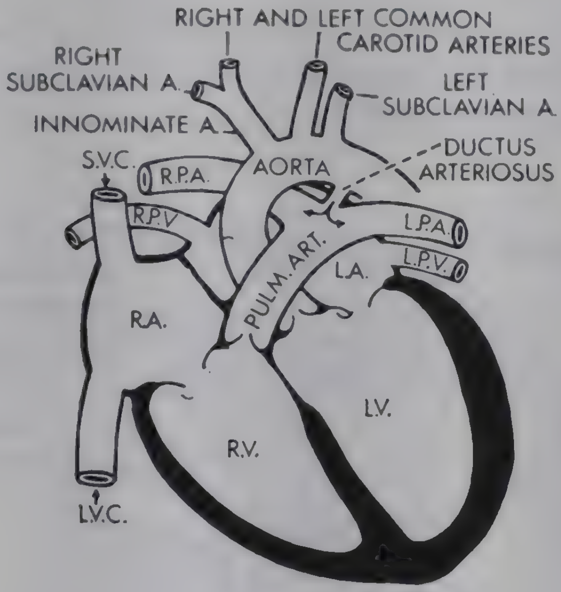


FIG. 51

PATENT DUCTUS ARTERIOSUS

Normally the ductus closes soon after birth but, for reasons which are obscure, this sometimes fails to take place. Since the pressure in the aorta is normally higher than that in the pulmonary artery there will be a continuous arterio-venous shunt, the volume of which depends on the size of the ductus. As much as 50 per cent of the left ventricular output may be passed through the lungs again with a consequent increase in the work of the heart.

The condition is much more common in females. Other congenital abnormalities may be associated.

Clinical Features. There may be no relevant symptoms for many years, but growth and development will be retarded if the defect is a severe one. In mild cases there will be no disability, but in cases of moderate severity dyspnoea on exertion and later the usual features of cardiac failure gradually develop.

A continuous 'machinery' murmur is heard with late systolic accentuation, maximal in the second left intercostal space near the sternum. It is frequently, but not always, accompanied by a thrill.

Enlargement of the pulmonary artery, but little enlargement of the heart, may be detected radiologically. The electrocardiogram is usually normal.

Treatment. In uncomplicated cases, the patent ductus can be divided with little risk, especially in children, and there is general agreement that this should be carried out in all cases, preferably before the child goes to school.

Prognosis. Death is usually from cardiac failure or infective endocarditis. Few untreated patients live beyond the age of 40. Following successful surgical treatment expectation of life is normal.

Coarctation of the Aorta

Narrowing of the aorta occurs in the region where the ductus arteriosus joins the aorta, i.e. just below the origin of the left subclavian artery (Fig. 52). The condition is more common in males.

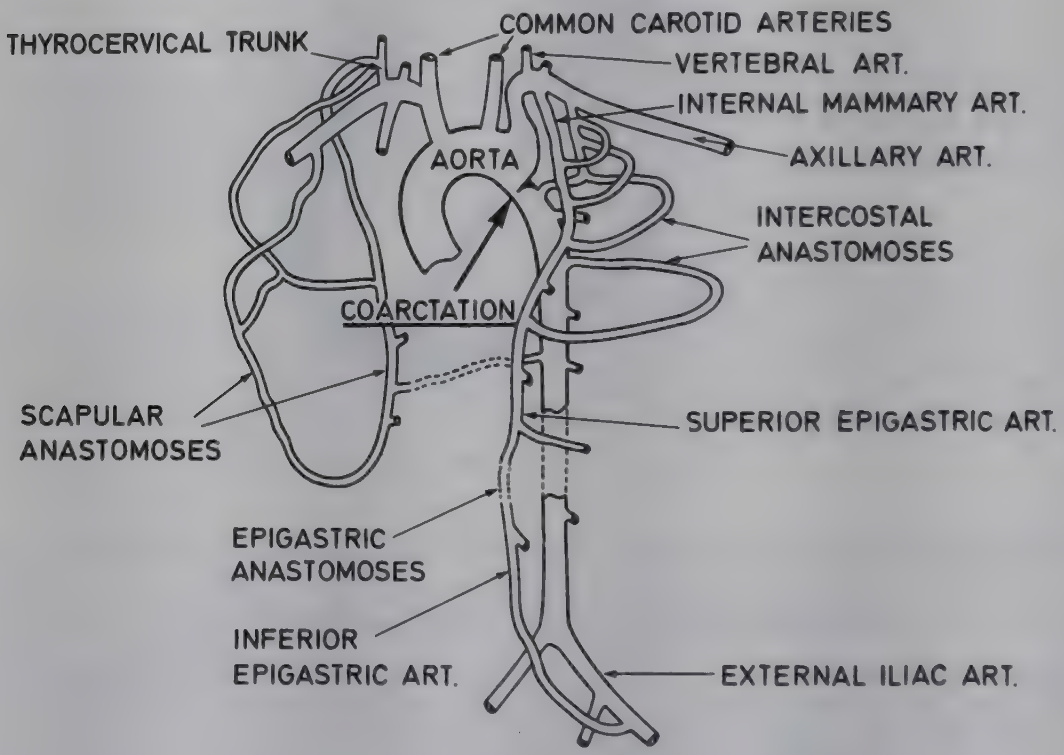


FIG. 52
COARCTATION OF THE AORTA

Clinical Features. Symptoms are often absent. Headaches and cardiac symptoms may occur from hypertension in the upper part of the body and occasionally weakness or cramps in the legs from decreased circulation in the lower part of the body.

The blood pressure is raised in the arms but is normal or low in the legs. Unduly large arterial pulsations may be visible in the neck. The femoral pulses are weak and delayed after the radial.

A systolic murmur is often present over the sternum but is usually loudest posteriorly.

Evidence of collateral circulation is present. Dilated, tortuous vessels exhibiting arterial pulsation may be visible or palpable around the scapulae or in the axillae, especially if the patient bends down.

Radiological examination in early childhood is often normal but at a later age may show changes in the contour of the aorta and notching of the under surface of the ribs from tortuous loops of enlarged intercostal arteries.

The electrocardiogram may show left ventricular hypertrophy.

Treatment. The constricted portion can be resected and the divided ends of the aorta anastomosed. Sometimes an arterial graft is necessary to bridge the gap. Surgical treatment is curative.

Prognosis. In untreated severe cases, death may occur from left ventricular failure, rupture of the aorta, cerebral haemorrhage or bacterial infection of the commonly associated bicuspid aortic valve.

Atrial Septal Defect

Atrial septal defect is more common in females. Since the pressure in the left atrium is normally higher than that in the right atrium, the shunt will be from left to right (Fig. 53). As a result there is gradual enlargement of the right side of the heart and of the pulmonary artery and its main branches. In time, the pressure in the right side of the heart may increase until the shunt is reversed.

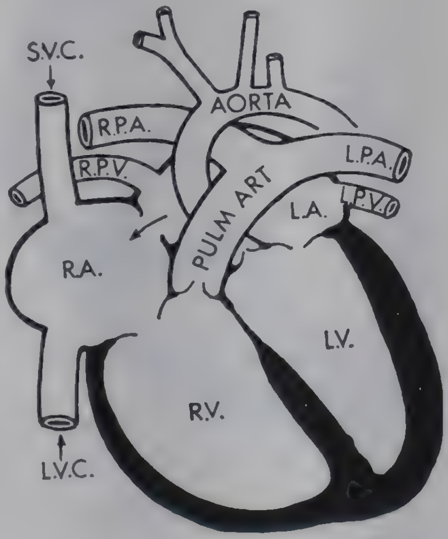


FIG. 53
ATRIAL SEPTAL DEFECT

Clinical Features. There may be no symptoms for many years. Dyspnoea, cyanosis and cardiac failure may develop. The characteristic physical signs are a pulmonary systolic murmur from increased blood flow and wide splitting of the second heart sound. Enlargement of the pulmonary artery and its main branches is seen radiologically and a dynamic pulsation observed on the screen ('hilar dance'). The right ventricular enlargement can also be seen and may be reflected in the electrocardiogram. Incomplete right bundle branch block is common.

Treatment. Surgical closure of a large defect should be carried out, preferably before the age of 10.

Prognosis. Most patients used to die in middle age from cardiac failure, but now, following surgical treatment, the expectation of life is probably normal.

Ventricular Septal Defect

Since the pressure in the left ventricle is higher than that in the right ventricle, the shunt is normally from left to right (Fig. 54).

Clinical Features. Usually there are no relevant symptoms. The characteristic signs are a harsh systolic murmur and thrill maximal in the fourth intercostal space to the left of the sternum. In many cases the defect is not sufficiently large to embarrass the circulation. In some the large volume load causes cardiac failure. In a few, severe pulmonary hypertension develops, the shunt reverses and cardiac failure may ensue.

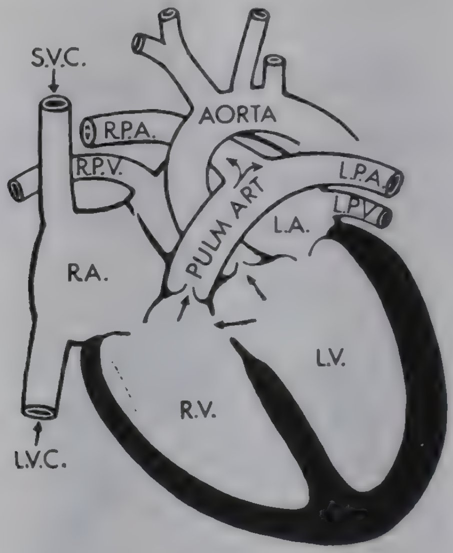


FIG. 54
VENTRICULAR SEPTAL DEFECT

Radiological and electrocardiographic examinations are normal except in the more severe cases when the heart is enlarged.

Treatment. The defect can be repaired by open heart surgery. Surgical treatment is not necessary for small defects and is dangerous if there is severe pulmonary hypertension. Antibiotic cover should be given for surgical procedures liable to produce bacteraemia.

Prognosis. This depends on the size of the defect. Duration of life may be unaffected, but in severe cases cardiac failure may develop at any age. Infective endocarditis is an occasional complication. Surgical treatment is curative if carried out before the heart is much enlarged.

Pulmonary Stenosis

Pulmonary stenosis may occur as an isolated anomaly in which case cyanosis may be absent, or in association with an atrial or ventricular septal defect in which case there may or may not be cyanosis depending on the relative pressures on the two sides of the shunt.

Stenosis may occur at the level of the pulmonary valve or in the infundibular region of the right ventricle.

Pulmonary Stenosis with Closed Interventricular Septum

Clinical Features. In many cases the stenosis is mild. In severe cases there may be dyspnoea, fatigue or, occasionally, syncope. The characteristic signs are a harsh systolic murmur and thrill, maximal in the second intercostal space to the left of the sternum. The pulmonary second sound is diminished. The pulmonary artery is usually dilated beyond the stenosis. The right ventricle is hypertrophied (Fig. 55). There may be an associated atrial septal defect.

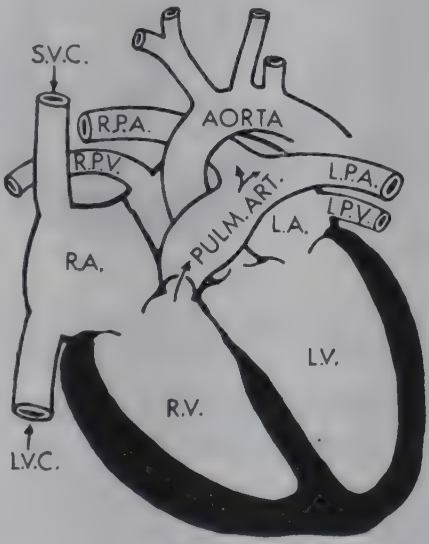


FIG. 55
PULMONARY STENOSIS

Treatment. In mild cases, no treatment is necessary. When the stenosis is severe, pulmonary valvotomy should be carried out.

Prognosis. Sudden death is liable to occur. When symptoms are progressive cardiac failure is inevitable unless surgical relief is possible.

Pulmonary Stenosis with Patent Interventricular Septum (Fallot's Tetralogy)

This is the most common form of cyanotic congenital heart disease in children or adults. The combination of lesions is (Fig. 56):

(*a*) Pulmonary stenosis.
(*b*) Interventricular septal defect.
(*c*) Dextro-position of aorta overriding the septal defect.
(*d*) Right ventricular hypertrophy.

Clinical Features. Dyspnoea and fatigue are the principal symptoms and the child characteristically assumes the squatting position. The principal signs are: cyanosis, polycythaemia and clubbing of the fingers; a loud systolic murmur, and often a thrill, maximal to the left of the upper sternum; soft pulmonary component of the second sound; enlargement of the right side of the heart; absence of the normal pulmonary artery curve on radiological examination.

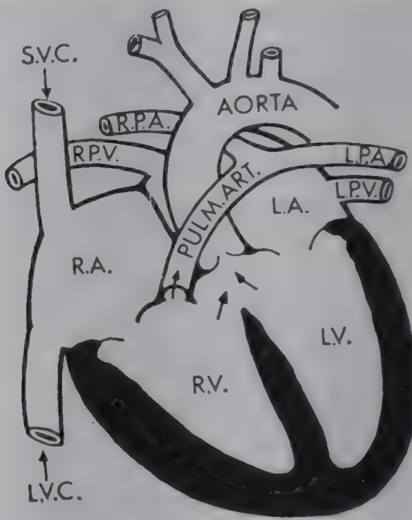


FIG. 56

FALLOT'S TETRALOGY

Treatment. In young children a palliative operation in the form of an anastomosis can be made either between the left or right pulmonary artery and the corresponding subclavian artery (Blalock's operation) or between the pulmonary artery and the aorta thereby increasing the blood supply to the lungs. Later total correction can be carried out using the by-pass technique.

Prognosis. Without surgical treatment few patients reach adult life. Correction abolishes symptoms. It is difficult to generalise about prognosis because the outlook depends on the degree of severity of the defect and the success of surgical treatment.

The Surgical Treatment of Heart Disease

Surgery plays an important part in the management of heart disease; it is now possible either to correct completely or to alleviate most types of congenital and rheumatic heart disease. It is also of value in many cases of ischaemic heart disease, infective endocarditis and constrictive pericarditis. Operations can often be performed under normal circulatory conditions with blood continuing to flow through the closed heart. Others require opening of the heart with temporary occlusion of the circulation (open-heart surgery). In such cases increased time for intracardiac surgery can be obtained either by cooling the blood or the whole body (hypothermia) and thereby decreasing the oxygen requirements of the tissues, or by the use of an extracorporeal circulation (pump oxygenator). In this latter technique venous blood is drained from the great veins into a reservoir and is then passed through an oxygenator and pumped back into the aorta or other major artery. The heart may then be stopped whilst an adequate circulation of the vital organs is maintained for several hours. The mortality of extra-corporeal circulation should be less than 1 per cent but patients subjected to this procedure have a relatively high risk of post-operative infection and blood disorders.

In certain cases, such as patent ductus arteriosus and atrial septal defect, complete correction can be achieved. In other cases, for example some instances of ventricular septal defect and coarctation of the aorta, prosthetic materials may be needed to effect a repair. In some types of disease of the heart valves, such as pure mitral stenosis, a satisfactory result may be obtained by a simple plastic operation. In others, the valve must be replaced either by a prosthesis or by a graft. Although many satisfactory results have been achieved with the use of prosthetic valves, they are liable to lead to complications which include thrombo-embolism and haemolysis. Because of the risk of thrombosis, patients with prosthetic valves are usually kept on anticoagulant therapy. Grafts may be of human origin (homografts). When such grafts are used; the risks of haemolysis and thrombosis are slight but the operations are technically more difficult and the long-term results remain uncertain. Furthermore, the supply of homografts is limited.

Heart Disease in Pregnancy

The management of heart disease in pregnancy is a more complicated problem than in the non-pregnant state and diagnosis may be difficult owing to the altered haemodynamics.

During pregnancy the blood volume increases by about 25 to 50 per cent due to retention of sodium by the body. The precise mechanism is unknown but may be endocrine in origin. The cardiac output also increases by about 25 to 50 per cent. Since the mean blood pressure does not alter, the work of the heart must be correspondingly increased. Slight enlargement of the heart may be present from the increased blood volume.

Pregnancy has no untoward effects on the normal heart but may inflict too great a burden on the diseased heart. Depending on the country concerned 50 to 90 per cent of all cases of heart disease in pregnancy are due to previous rheumatic fever and most of these have mitral stenosis. Congenital heart disease and hypertension account for most of the remainder.

It is important to emphasise that any assessment based on the severity of symptoms is unreliable and potentially dangerous. A woman with mitral stenosis may be symptomless early in pregnancy but die from a first attack of pulmonary oedema in the later months. Severity should be assessed on objective grounds. In these days of planned families, the opportunity may be provided of giving advice before the patient becomes pregnant.

If signs of cardiac failure are, or have at any time been, present, pregnancy is not advisable unless valvotomy has been successfully carried out. This rule applies even if the failure can be readily controlled, for the risk will be considerable to both mother and child. An exception may occasionally be allowed if the mother is extremely anxious to have a child and she and her husband are willing to take the risk; but there must be reasonably good cardiac compensation. Active rheumatic fever and infective endocarditis are definite contra-indications. If there is no evidence of failure, the rhythm is normal, there is little or no dyspnoea and no great enlargement of the heart or signs of tight stenosis and the patient can be kept under close observation, then there is little added danger from pregnancy to a patient with mitral stenosis. Women with rheumatic heart disease should be advised to plan their pregnancies when they are young; they should be discouraged from having more than two children. The strain of having another child to look after may well prove greater than that of the pregnancy itself. Also most women with rheumatic mitral disease tend to develop atrial fibrillation by the age of 35 to 40, and the combination of fibrillation and the extra work entailed in looking after a toddler may be serious. Economic factors are most important in that domestic help will allow the mother more adequate rest.

Although termination of pregnancy is a relatively minor matter in the early months the problem is very different later because an abdominal operation is necessary. Under medical supervision and treatment, continuation to term, or until the child is viable and labour can be induced, is usually preferable. Natural delivery is probably safer than Caesarean section.

The best safeguard is repeated observation. By this means the progression of doubtful or manifest signs of cardiac failure may be detected at an early stage and appropriate treatment instituted. In such cases a period of rest in bed is important. Domestic help should be arranged if possible and extra rest is advisable during the day. Digitalis, diuretics and salt restriction will be indicated if failure is present. Acute respiratory infections should be promptly treated as they may precipitate cardiac failure. Mitral valvotomy can be carried out if necessary during pregnancy but operative intervention is rarely required if adequate medical treatment is given.

The periods of greatest danger are the last three months and the first two days after delivery. At these times cardiac failure is particularly liable to occur. A post-partum injection of ergometrine may be dangerous if heart failure has been present; pulmonary oedema may result from the consequent increase in circulating blood volume.

Cardiac Neurosis

Effort syndrome was the term generally applied in this country to a condition known in the United States as neuro-circulatory asthenia but which is now recognised as being a form of anxiety neurosis. The condition is difficult to define, but may be recognised by a characteristic series of symptoms and signs suggesting overactivity of the autonomic nervous system due to emotional factors.

Predisposing and Precipitating Factors. These are similar to any anxiety neurosis and are discussed on page 919. The subjects tend to be diffident, solitary, introspective and anxious. They are particularly averse to military service and fear is frequently responsible for this.

Clinical Features. Symptoms include breathlessness, nervousness, fatigue, palpitation, left mammary pain, dizziness, headache and sweating. Left mammary pain is apt to be mistaken for angina pectoris, an error which may be responsible for unnecessary invalidism. The pain is not felt across the middle of the chest, as in ischaemic heart disease, but in the neighbourhood of the left breast. It is described as a dull ache which persists for hours or even days and is often accompanied by sharp, shooting or stabbing pains. The relationship to exertion is indefinite and inconstant. The pain is more likely to follow than accompany effort but may occur at any time, even in bed.

Breathlessness is out of proportion to the amount of exertion undertaken and is often present at rest. There is a sensation of inability to take a full or satisfactory breath and a deep sighing type of respiration is a characteristic feature. By contrast breathlessness at rest of cardiac origin would indicate serious disease for which an obvious cause would be present.

Signs include tachycardia, sweating, flushing, tremor and an obviously nervous manner. The hands are often cold and blue despite moist palms. Axillary sweating is also characteristic. There is no evidence of organic disease in the heart or any other system.

Differential Diagnosis. A thorough clinical examination supplemented by radiological examination of the heart and lungs will exclude most conditions liable to be mistaken for effort syndrome, e.g. valvular disease, hypertension and pulmonary tuberculosis. The diagnosis of effort syndrome should not be made on the negative basis of excluding disease but on the positive evidence of recognising the syndrome.

Treatment. An initial thorough physical examination is essential but should not be repeated. Reassurance that the heart is healthy is most important. Sympathy and understanding, explanation and encouragement should be given in due proportion. Expert psychological help may be necessary.

DISEASES OF ARTERIES

For clinical purposes it is convenient to classify arterial disease under the general headings of degenerative, inflammatory and vasospastic causes.

DEGENERATIVE ARTERIAL DISEASE

The two main types of degenerative arterial disease are arteriosclerosis and atherosclerosis.

Arteriosclerosis

Arteriosclerosis is a term which in the past has been applied rather indiscriminately to various unrelated forms of arterial disease. Its retention is justified only if it is confined to the degenerative changes which are part of the normal ageing process and which affect the whole arterial tree. These changes involve the middle coat and later the intima of the vessel.

Medial or Mönckeberg's sclerosis is the name given to degenerative changes which occur in old age in the muscular coats of medium sized arteries such as the radial. Calcification of the media is the characteristic change and accounts for the 'pipe stem' arteries so commonly palpable in the elderly and of no clinical significance. Since the medium and large vessels are mainly affected and their lumina are not greatly reduced in size, clinical features are usually absent.

Atherosclerosis

Atherosclerosis is a condition which principally affects the aorta, large arteries and certain medium-sized vessels, particularly the coronary and cerebral arteries. It becomes increasingly common as age advances, but it is not an inevitable concomitant of ageing, and there is a great variation in its extent and severity. Although often associated with and accelerated by hypertension, atherosclerosis may be advanced even in the presence of a normal blood pressure. It may also occur in response to a local rise of pressure in the pulmonary arteries of patients with pulmonary hypertension. The pulmonary artery is not otherwise subject to atherosclerosis.

Pathology. The basic atheromatous lesion is the plaque, the most important constituents of which are cholesterol and other lipids which may be free in the intimal tissues or inside cells. At a later stage the plaque becomes sclerosed and calcified. Thrombosis is liable to occur on the surface of the plaque, particularly if it ulcerates. Embolism is frequent.

During life atherosclerosis is recognised by its effects on function, but the absence of clinical features does not exclude its presence, even in severe degree, in many persons who are apparently in good health. When narrowing of a vessel occurs, serious impairment of the blood supply to important structures may result. Coronary atherosclerosis, for example, is responsible for angina pectoris, cerebral atherosclerosis for many mental changes in old age, and atherosclerosis in the vessels of the legs may be responsible for intermittent claudication. The affected vessels are liable to thrombosis and thrombo-embolism and this may result, for example, in cardiac infarction, hemiplegia or gangrene. A damaged arterial intima predisposes to thrombus formation, but the actual cause of the initial lesion is uncertain.

In the aorta and its main branches there is widening due to replacement of elastic by fibrous tissue.

The pathogenesis of atherosclerosis is discussed in its context of ischaemic heart disease on page 265.

Atherosclerosis Obliterans

This condition affects males more commonly than females and most cases occur after the age of 50. Atherosclerosis is rarely seen in the upper limbs. It is particularly common in diabetes.

Symptoms. The principal symptoms which follow impairment of blood supply to the extremities are (1) pain, which occurs on exercise (intermittent claudication) and (2) cold extremities. Although the pathological changes are usually present in both lower limbs, symptoms commonly present only on one side.

By intermittent claudication is meant pain which develops on exercising a limb and disappears with rest. It most commonly occurs in the calf on walking. The pain is due to relative ischaemia of the muscles. Pain occurring at rest signifies severe ischaemia. Pain which is relieved by elevation of the part suggests venous obstruction, and pain which is relieved by dependency suggests gross arterial obstruction. Affected patients seldom die from peripheral vascular disease but frequently succumb to myocardial infarction.

Clinical Features. Ischaemia may lead to dryness, scaling and inelasticity of the skin, loss of hair and brittle nails. There may be a change of colour of the skin, delay in the return of colour after blanching with light finger pressure, ulceration or gangrene. Where gross lesions are present in one limb, the lower temperature can be recognised by simple palpation.

If the ischaemic limb is first raised 75 degrees above the horizontal, it will blanch more quickly than normal. If then placed in the dependent position, there will be delay in venous filling and in flushing.

Loss of pulsation of one or more peripheral arteries is a common and important feature of arterial disease; bruits may be heard over the larger arteries if they are partially obstructed.

Investigative Techniques. Where there are good facilities for arteriography, reactive hyperaemia and oscillometry are now little used. Research techniques include the use of ultrasonic blood flow detectors, clearance measurements using isotopes and electromagnetic metering.

REACTIVE HYPERAEMIA. The limb is raised to 45 degrees above the horizontal until the blood is drained out. The foot is rapidly flexed and dorsiflexed until pallor occurs. The limb is then placed in the dependent position. The normal limb should flush down to the extremity within about 10 seconds. In obliterative vascular disease there may be a delay of several minutes.

OSCILLOMETRY. The approximate level of arterial occlusion may be ascertained by means of an apparatus which measures arterial pulsations.

PRESSURE MEASUREMENTS BY ULTRASOUND. The peripheral artery is located by Döppler ultrasound; a cuff is inflated round the ankle or wrist until the pulse disappears. The cuff is slowly deflated until blood flow produces a signal; that represents systolic pressure. Pressure so determined should be compared with that in the brachial artery determined by sphygmomanometry.

Radiology

1. *Radiography.* Calcification will be shown if present. Calcification is especially common in Mönckeberg's sclerosis but does not necessarily indicate that the arterial lumen is significantly narrowed.

2. *Arteriography*. Intra-arterial injection of a radio-opaque solution will show the site of vascular occlusion and the extent of the collateral circulation, if present.

Treatment. Until the pathogenesis of atherosclerosis has been clearly established and until specific measures are discovered which are accepted as being effective for its prevention and cure, the treatment of peripheral vascular disease must continue to be unsatisfactory. If diabetes is present it should be treated on the usual lines (p. 686), and this also applies to obesity (p. 177). Smoking should be forbidden.

LOCAL MEASURES. Cold should be avoided and suitable woollen clothing worn, especially on the limbs. The application of heat to the affected limb is harmful because whilst it raises the local metabolism, the blood flow cannot be correspondingly increased. Pain at rest may be reduced by raising the head of the bed or by lowering the limb below the horizontal and keeping it cool.

Protection against trauma and the early treatment of sepsis is most important. Fungal infection between the toes should always be treated. Detailed instructions on the care of the feet and nails must be given. The feet should be kept scrupulously clean, carefully dried after washing, especially between the toes, and dusting powder containing zinc oxide and salicylic acid applied. Nails should be cut carefully and corns pared with caution. It is wise to employ the services of a chiropodist. Socks and shoes should be well fitting. Even the slightest abrasion should be taken seriously and medical advice sought. Dressings to keep the part dry are required for any breach of surface.

Areas of gangrene should be kept clean and dry until a clear line of demarcation appears. Thereafter surgical treatment will be required.

MEASURES TO IMPROVE THE BLOOD SUPPLY

(*a*) *Regular exercise* encourages the development of collateral vessels. Patients should not be alarmed by the development of pain and they should be encouraged to believe that with exercise and the stopping of smoking improvement is expected and that the occurrence of gangrene is improbable.

(*b*) *Buerger-Allen Exercises*. The legs are raised and supported 45 degrees above the horizontal for one minute (or until blanched), then lowered over the side of the bed or couch for a minute until thoroughly pink. While still dependent the feet are dorsiflexed and plantarflexed alternately and the toes are moved repeatedly for two minutes. This cycle is repeated four to six times, three or four times a day.

(*c*) *Drugs*, including vasodilators, are usually of little value even when an element of spasm is present.

(*d*) *Surgical Measures*. Sympathectomy may be of value when the limb is cold or rest pain is present but it does not help claudication. Direct arterial surgery is indicated for disabling claudication, rest pain or gangrene provided the vessels are shown by angiography to be amenable to reconstruction.

Sudden Occlusion of a Major Artery

This may result from thrombosis or embolism. The limb becomes painful, cold, numb and pale, and pulses distal to the block are absent. The outcome depends on the collateral circulation and on subsequent treatment. Pain should be relieved and the limb kept at rest and exposed to room temperature. The other limbs and body should be kept warm and reflex vasodilatation encouraged by an electric blanket or hot-water bottles to the trunk.

Embolectomy should be considered whenever a major artery (for example, brachial or popliteal) is occluded; the early intervention of a surgeon skilled in this field is important. Heparin should be given intravenously (p. 309). Amputation for gangrene may be necessary.

Atherosclerosis and Aneurysm Formation

Atherosclerosis is frequently present in the aorta but seldom affects its function. It may, however, be responsible for aneurysms of any part of this vessel. An aneurysm in the ascending portion may cause pain because of erosion of the ribs or sternum; a pulsating mass may occasionally be visible. Syphilitic aortitis (p. 304) may also cause an aneurysm at this site. An aneurysm of the arch of the aorta may produce wheezing or hoarseness from its effect on the trachea and recurrent laryngeal nerves. Situated in the descending aorta an aneurysm may produce pain because of encroachment on the vertebrae, ribs or nerves. Once symptoms have developed, the prognosis is usually poor and there is a substantial risk of rupture. Surgery should be considered, but the results are often not good because of co-existing coronary or cerebral disease.

Dissecting Aneurysm of the Aorta

In this condition a tear occurs through the intima secondary to degeneration of the media. As a result blood makes its way in a split in the media to form a new channel. Death usually occurs from rupture through the adventitia into the pericardium or elsewhere. Some patients are hypertensive. In women it may occur with pregnancy.

Dissecting aneurysm may also occur in Marfan's syndrome in which there is loss of elastic fibres in the media as part of a generalised disorder of connective tissue; long thin extremities and subluxation of the lens are other characteristics.

The onset is sudden with severe, tearing, chest pain which often radiates into the neck, back, abdomen or into the legs. It may be precipitated by exertion. In some cases the condition may simulate myocardial infarction. The heart sounds, however, are unchanged and the blood pressure is maintained, unless shock is present. Neurological features may result from occlusion of branches of the aorta supplying the spinal cord. One or more of the peripheral pulses may be obliterated.

Diagnosis. This is suggested by the characteristics of the pain described above and the absence of the ECG and enzyme abnormalities of myocardial infarction. The chest radiograph may be helpful in showing a broadened mediastinum due to widening of the aorta.

Treatment. In the initial stages the blood pressure should be lowered by antihypertensive drugs to normal levels. Surgical treatment is usually necessary later.

INFLAMMATORY ARTERIAL DISEASE

The principal types of inflammatory arterial disease are:

1. Syphilitic aortitis.
2. Thrombo-angiitis obliterans.
3. Polyarteritis.
4. Cranial (giant cell) arteritis.
5. Takayashu's syndrome (pulseless disease).

Syphilitic Aortitis

Syphilitic aortitis is much rarer in Britain than it was 30 years ago but is still an important cause of ill-health in many parts of the world. There is often a latent period of 15 to 20 years following infection before clinical manifestations are evident in the cardiovascular system. Neurosyphilis not infrequently co-exists.

Pathology. The disease begins just above the aortic valve cusps. In the adventitia there is infiltration of lymphocytes and plasma cells round the vasa vasorum, which are obliterated by intimal proliferation. Elastic tissue is gradually replaced by fibrous tissue and this leads to dilatation of the aorta. Proliferation of the intima occurs and may involve the mouths of the coronary arteries leading to myocardial ischaemia, or spread along the valve cusps which become thickened, everted and incompetent.

The macroscopic changes are characteristic and consist of bluish-grey raised intimal plaques and longitudinal wrinkling of the inner surface of the aorta. Atheromatous changes with calcification are frequently associated.

Clinical Features. Syphilitic aortitis occurs most frequently between the ages of 40 and 55.

AORTIC REGURGITATION. The clinical manifestations are similar to those resulting from rheumatic aortic regurgitation (p. 256). In the absence of other evidence of rheumatic heart disease, e.g. mitral stenosis, and especially in men between the ages of 30 and 60, syphilis should be excluded as a possible cause of aortic regurgitation by taking blood for a Wassermann or VDRL test.

ANGINA PECTORIS is due to coronary ostial stenosis. Sudden death is particularly liable to occur. It must be remembered that there are causes of angina pectoris other than coronary atherosclerosis.

AORTITIS. This diagnosis is difficult in the early uncomplicated stages. Suspicions may be aroused by an aortic systolic murmur, together with accentuation of the second sound. Dilatation and calcification of the ascending aorta may be demonstrated by radiological examination.

AORTIC ANEURYSM. When due to syphilis, aneurysms are most common in the proximal parts of the thoracic aorta. In contradistinction, atheromatous aneurysms are most common in the distal portions. The clinical features depend on the precise situation. Symptoms may arise from pressure on neighbouring structures and signs are similar to those of an expanding mediastinal tumour. There may be considerable difficulty in differential diagnosis as pulsation may be transmitted by a tumour from a normal aorta, and an aneurysm may not pulsate owing to obliteration of the cavity by blood clot.

Treatment. If antisyphilitic drugs are given in the early stages of the infection cardiovascular manifestations in later life are prevented. Treatment of syphilitic aortitis consists of a single course of procaine penicillin, i.e. 600,000 units daily for 10 days. If cardiac failure is present this should first be controlled. Surgical treatment may be indicated for aortic regurgitation or aneurysm.

Thrombo-angiitis Obliterans

(BUERGER'S DISEASE)

This uncommon condition is of obscure origin. It usually begins before the age of 40 and is almost confined to males. Cigarette smoking is an important aetiological factor. The lower limbs are principally affected. The wall of the artery is infiltrated with polymorphs and the lumen may be obstructed by clot. The adjacent vein is often involved.

The symptoms and signs are essentially those of diminished blood supply to the limb (p. 301); persistent pain in a cold, cyanosed toe is often the presenting complaint. This is followed by intermittent claudication and rest pain. In the leg, atrophic changes and finally gangrene may develop. Involvement of the veins may cause thrombophlebitis migrans.

There is no specific treatment but it is essential that cigarette smoking is stopped.

Polyarteritis

This is an uncommon condition of unknown aetiology, most often seen in men between the ages of 20 and 50. It may be regarded as a connective tissue disorder, allergic in origin. In some patients it appears to be due to hypersensitivity to serum or to drugs such as penicillin and sulphonamides. The characteristic lesions consist of multiple nodules on the smaller arteries. The vessel wall is infiltrated by polymorphs and necrosis follows with resultant aneurysmal dilation. Thrombosis may occur.

Clinical features such as fever, tachycardia, wasting, sweating and generalised pain are accompanied by local manifestations of ischaemia in various parts of the body. The vessels of the kidney, gastrointestinal tract, heart, peripheral nerves and skin are particularly affected giving rise to such varied manifestations as haematuria, abdominal pain, angina, pericarditis, peripheral neuritis, subcutaneous nodules or localised oedema. Involvement of the lungs may cause asthma. There may be leucocytosis or eosinophilia. Hypertension is usual at some stage. The course is usually progressive but mild cases may recover. There is no curative treatment, but corticosteroids are worthy of trial. Administered before vascular damage is too extensive, they may produce a remarkable remission. The outlook in more advanced cases is less hopeful. The fibrosis which follows healing of the vascular lesions may be sufficiently extensive to lead to myocardial infarction or renal failure.

Cranial Arteritis

(GIANT CELL ARTERITIS)

Cranial arteritis may be related to polyarteritis or to polymyalgia rheumatica (p. 782) but it is a distinct clinical entity which is so named because the striking clinical finding is tender, thickened cranial arteries. The cause of the disease is unknown.

The vessel wall is infiltrated by mononuclear cells, plasma cells and giant cells. Thrombosis may occur. The vessels of the scalp, particularly the temporal arteries, are usually affected but other arteries may also be involved, for example those of the retinae and brain, and the condition may be widespread throughout the body.

Intense headache and sometimes blindness are prominent features. General systemic manifestations include fever, malaise, arthralgia, anorexia, weakness and loss of weight. It affects elderly persons, and usually ends in recovery after several months. There is no specific treatment, but corticosteroid therapy is of great symptomatic value and may prevent complications such as blindness.

Takayashu's Syndrome

(PULSELESS DISEASE)

This is a disorder which predominantly affects young females. An arteritis involves the aortic arch with narrowing of its major branches. The pulses are diminished in the upper extremities, neck and head. Headache, syncope, visual disturbance and muscular wasting may occur. The prognosis is poor but corticosteroids are sometimes of value.

VASOSPASTIC DISORDERS

Raynaud's Phenomenon

Raynaud's phenomenon is the name given to a peripheral vascular disturbance consisting of spasmodic contraction of the digital arteries, which is precipitated by cold, emotion and by other causative factors mentioned below. Primary Raynaud's phenomenon usually starts in childhood and may occur in either sex, being no more than an exaggerated physiological response to cold. The term 'secondary Raynaud's phenomenon' is used to describe the disorder which occurs secondary to pressure of a cervical rib, to obliterative arterial disease, to certain occupations in which the arms and hands are exposed to high frequency vibrations from pneumatic drills, polishing tools, etc. or occasionally to cold agglutinins and cryoglobulins. It may also occur in disorders of connective tissue, especially scleroderma. The changes are virtually confined to the digits. Severe forms may lead to secondary changes in the arterioles and ultimately to gangrene.

Pathogenesis. This is uncertain. There is evidence of increased vasomotor tone in some cases; in others it is normal and the smooth muscle of the arterioles appears to be abnormally susceptible to cold.

Pathology. In the early, uncomplicated stages, there are no pathological changes. Later obliterating endarteritis occurs, often with thrombosis in the lumen. Prolonged asphyxia will lead to ischaemic changes in the skin of the digits and nails, superficial necrosis and finally gangrene.

Clinical Manifestations. Mild forms are common in both sexes as the familiar 'dead fingers'. Symptoms are usually bilateral and fingers are more affected than toes, beginning at the extremities. Paraesthesiae, e.g. numbness, tingling and burning, are more prominent than pain. Sensitivity to cold may be extreme and disabling.

Colour changes usually consist of three phases: pallor, cyanosis and redness. If the limb is bloodless it will be pale. If blood flow is sluggish excessive deoxygenation results in cyanosis. Redness is a rebound phenomenon due to excessive vasodilatation (reactive hyperaemia) which may follow spasm.

Diagnosis. It is important to recognise the presence of any underlying disease, as discussed above. It should be differentiated from acrocyanosis which occurs mainly in young women whose hands are persistently cold and sweaty, go blue on exposure to cold and flush on warming. Chilblains are often also present.

Treatment. Vasodilator drugs may be tried, but the results are very disappointing. Protection from cold is all-important. In severe cases, sympathectomy, to remove vasomotor tone, should always be considered, but the long-term results are often disappointing. Smoking should be given up.

DISEASES OF VEINS

Venous Thrombosis

(PHLEBOTHROMBOSIS; THROMBOPHLEBITIS)

A distinction may be made between thrombophlebitis when the endothelium is injured by inflammation, and phlebothrombosis when clotting is the primary disturbance. The latter is the more common condition and the more dangerous because of the greater risk of pulmonary embolism.

Aetiology. The following factors are of importance in causing venous thrombosis.

1. *Slowing or Obstruction of the Blood Stream.* This may result from rest in bed, especially in the elderly or when a faulty position is assumed, as when a pillow is placed under the knees and the calves are compressed. Cardiac failure also leads to slowing of the circulation.
2. *Injury to the Endothelium of the Vessel Wall.* This may be due to trauma and may follow accidents, operations, childbirth, intravenous infusions or injections.
3. *Increased coagulability of the Blood.* Many factors may disturb the dynamic equilibrium that normally exists between coagulation and fibrinolysis, notably an increase in platelet adhesiveness. This may occur for example in malignant disease or with the use of the contraceptive pill. An increased liability to thrombosis also occurs in dehydration and polycythaemia due to an increase in the blood viscosity.

Pathology. The primary thrombus consists mainly of dense layers of platelets and fibrin whereas the secondary clot consists of a loose friable jelly-like mass of fibrin and red cells which readily becomes detached to form an embolus. After a few days inflammatory changes occur in the wall of the vein. The clot may undergo lysis or organisation.

Venous thrombosis is most common in the lower limbs, particularly in the venous sinuses of the soleus muscle in the calf and in the femoral and iliac veins. Superficial thrombophlebitis most commonly occurs in the saphenous vein more particularly if there are associated varicosities. Phlebothrombosis occurs much less frequently in the upper limb but the axillary vein may be involved as a complication of trauma, neoplasm or radiotherapy.

Suppurative thrombophlebitis is a rare but very serious condition usually involving the veins of the abdomen or pelvis following sepsis.

Clinical Features. The patient may complain of pain in the calf but the process is often silent and undiagnosed. An unexplained slight pyrexia may be the only warning. If the lumen of a main vein is occluded, there is dilatation of the superficial veins, a slight temporary rise in the temperature of the leg, and, later, oedema of the ankle. In extensive occlusive ilio-femoral thrombosis the whole lower limb is swollen and white if the collateral channels remain patent. If the collaterals are also occluded, the leg is blue—a pregangrenous condition. In contrast there may be no signs in the presence of an extensive non-occlusive, potentially lethal clot. Pulmonary embolism is frequently the first clinical manifestation of venous thrombosis.

Diagnosis. The most certain way of establishing the diagnosis is by phlebography. The veins from the ankle to the inguinal ligament can be demonstrated by ascending lower limb phlebography—a relatively straightforward procedure. Percutaneous iliofemoral phlebography may also be required. Other techniques which are of value, though not available generally, are the uptake of ^{125}I labelled fibrinogen and ultrasound. The former is used for the early detection of thrombosis, for example post-operatively. Ultrasound is used to assess the patency of deep veins in patients who present with a swollen leg or with pulmonary embolism.

Prophylaxis. Efforts must chiefly be directed to the prevention of venous stasis. This is easiest in surgical patients when the period of risk can be defined. Almost all post-operative thromboses begin during or within 72 hours of operation. Early ambulation should be encouraged after surgery and medical illnesses. This means more than simply transferring the patient from lying in bed to sitting in a chair. Active exercises should be prescribed and at other times the leg should be elevated. An elastic support should be worn if the patient is at particular risk. If confinement to bed is unavoidable, the patient should be encouraged to move the lower limbs frequently. In hospital, exercises can be organised under the supervision of a physiotherapist. Faulty posture in bed must be corrected, tight bandages avoided and cardiac failure and dehydration should receive attention.

For patients at particular risk other prophylactic measures include low dose subcutaneous heparin and intravenous dextran 70; the latter lowers blood viscosity and reduces platelet adhesiveness.

Treatment. The aim of treatment is to prevent propagation of the clot and pulmonary embolism, damage to the valves of the vein and chronic venous insufficiency. These objectives are best achieved by heparin. The role of oral anticoagulants is to prevent recurrences by longer term treatment.

Unless there is an obvious contraindication, such as active peptic ulceration or a bleeding surface as after prostatectomy, treatment is initiated with heparin and continued with warfarin. Heparin is preferably given for 7-10 days by intravenous infusion or, ideally, by an infusion pump in a dose of 25,000-40,000 units daily controlled by a clotting time of twice or thrice normal. Alternatively, 10,000 units may be given every 6 hours by intravenous injection. If bleeding occurs, it usually stops when heparin is withdrawn. Protamine sulphate (10-30 mg i.v.) is a specific antidote to heparin but is rarely required.

For longer term treatment warfarin is preferable to phenindione as hypersensitivity reactions are common with the latter. A single dose of 20-40 mg is given and the prothrombin time measured on the third day, the aim being a value of 2-2½ times that of a control. The maintenance dose of warfarin varies from 1 to 10 mg daily. The oral anticoagulant should be continued for at least one month and for six months if there has been gross swelling of the legs. The risk of haemorrhage is increased as control is difficult if there is liver disease, or if the patient is also taking phenylbutazone, salicylates or clofibrate. The abrupt withdrawal of phenobarbitone is also dangerous as this drug promotes the breakdown of warfarin (p. 531). Vitamin K_1 (10-20 mg i.v.) is the specific antidote for warfarin overdosage.

Thrombolytic therapy with streptokinase is expensive but is under trial for ilio-femoral thrombosis. Thrombectomy should occasionally be considered for a recent non-occlusive thrombosis at this site.

The legs should be elevated to 15° and physiotherapy commenced after 48 hours. Constipation or other activity involving straining must be avoided in view of the danger of pulmonary embolism in such circumstances.

The venous flow is accelerated by the support of tapered elastic hose but care must be taken to avoid a constricting effect by the hose rolling up. The ambulant woman should wear elastic support tights and for men below-knee elastic hose is best. Support of this kind will probably be necessary permanently after a severe thrombosis to control chronic venous insufficiency.

Superficial thrombophlebitis usually responds to an elastic support and phenylbutazone in a dose of 200 mg thrice daily for about one week. There may be complicating deep venous thrombosis, particularly if the proximal saphenous vein is involved. Then anticoagulants will be required.

PREVENTION OF CARDIOVASCULAR DISEASE

Congenital Heart Disease. The causes of congenital heart disease are still obscure. Heredity cannot be a significant factor as congenital heart disease does not often run in families.

Rubella contracted by the mother during the second or third month of pregnancy is frequently followed by the development of congenital cardiac lesions in her child. Rubella is prevented by the vaccination of young girls in their early teens.

Rheumatic Heart Disease. In Britain the incidence of rheumatic fever is falling due to improvement in social conditions of the lower income groups and to the therapeutic control of streptococcal infection. Since recurrences are common following a first attack of rheumatic fever, prophylatic chemotherapy (p. 262) is indicated in adolescents.

Infective Endocarditis. This condition occurs especially in persons who suffer from congenital heart disease or from rheumatic valvular disease. In both cases patients with mild lesions and little disability are as susceptible as those with gross lesions and are liable to become infected during transient low-grade bacteraemia such as often occurs during removal of teeth or tonsils or operations on the urinary tract. Penicillin should be used in susceptible persons to provide 'cover' for even minor operations which may result in transient bacteraemia.

Cardiovascular Syphilis. The primary syphilitic infection may be masked by prompt treatment for gonorrhoea without subsequent surveillance. Thorough treatment of all cases, education of the public to recognise the risk of neglecting the facilities for treatment which are available in all large centres, and social efforts to combat the causes which result in the spread of venereal disease are the means which will prevent cardiovascular syphilis.

Thyrotoxic Heart Disease. Cardiac complications can be avoided by early diagnosis and adequate treatment of thyrotoxicosis.

Hypertension and Atherosclerosis. An annual medical examination, for those in the middle years of life, though having the disadvantage of provoking introspection in some instances, has the advantage that hypertension can be recognised in its early stages and appropriate treatment instituted. At the same time the individual may be recognised who is at risk and preventive measures instituted as advised on page 272. The time spent in counselling in this way often helps the patient to recognise the need for fundamental changes in his way of life if health is to be preserved.

D. G. JULIAN.
R. W. D. TURNER.

Further reading:

Goldman, M. J. (1973). *Principles of Clinical Electrocardiography*. 8th ed. Los Altos, California: Lange.
Holling, H. E. (1972). *Peripheral Vascular Diseases*. Philadelphia: Lipincott.
Hurst, J. W. & Logue, R. B. (1970). *The Heart*, 2nd ed. New York: McGraw-Hill.
Julian, D. G. (1973). *Cardiology*, 2nd ed. London: Baillière & Tindall.
Matthews, M. B. (1973). Examination of the cardiovascular system. In *Clinical Examination*, 3rd ed., edited by Macleod, J. Edinburgh and London: Churchill Livingstone.
Turner, R. W. D. (1972). *Auscultation of the Heart*. Edinburgh and London: Churchill Livingstone.

Diseases of the Respiratory System

ANATOMY

THE respiratory system is divided for descriptive purposes into the upper and lower respiratory tracts, the dividing line being the lower border of the cricoid cartilage. This division is an arbitrary one and must not be allowed to obscure the intimate relationship of upper respiratory disease to disease of the bronchi and lungs. For example, an upper respiratory infection such as sinusitis may under certain conditions give rise to bronchitis or even to pneumonia. Conversely, lung disease may be responsible for disease in the upper respiratory tract, as in the case of tuberculous laryngitis complicating pulmonary tuberculosis.

THE UPPER RESPIRATORY TRACT

The upper respiratory tract, which includes the nose, nasopharynx and larynx, is lined by vascular mucous membrane covered by ciliated columnar epithelium. The rich blood supply ensures that the inspired air enters the lungs at body temperature and fully saturated with water vapour. The *cilia*, aided by the layer of sticky mucus covering them, have the important function of trapping foreign particles and bacteria, and propelling them towards the pharynx. The whole respiratory epithelium down to the terminal bronchioles is equipped with cilia, which probably play an important part in the prevention of respiratory infection.

The *nasal sinuses* communicate with the nasal cavities by narrow openings and are frequently involved in nasal and nasopharyngeal infections. Adequate drainage of infected sinuses is often prevented by inflammatory oedema of the mucosa lining their narrow openings: as a result, resolution of sinus infection is often slow and sometimes incomplete.

The *larynx*, in addition to being the organ of voice production, has the function of preventing particles larger than can be dealt with by the cilia from reaching the lower respiratory tract. This it does by means of the *cough reflex*. The larynx is often involved in disease, particularly infection. It is sometimes obstructed by oedema or exudate, or by an impacted foreign body. *Laryngeal paralysis* (p. 384) is usually due to a lesion of the recurrent laryngeal branch of the vagus nerve. As the left recurrent laryngeal nerve runs part of its course within the thoracic cavity, in close proximity to the aortic arch and the left pulmonary hilum, a bronchial carcinoma in the left hilar region and, less frequently, an aortic aneurysm may cause paralysis of the left vocal cord. Paralysis of the right vocal cord is rare, most cases being due to an aneurysm of the right subclavian artery.

THE TRACHEA, BRONCHI AND LUNGS

The *trachea* begins at the cricoid cartilage and ends at the level of the sternal angle by bifurcation into the two *main bronchi*. The trachea is usually palpable in the suprasternal notch, where in normal subjects it is exactly in the midline.

Deviation of the trachea to either side, in the absence of a local lesion in the neck, is a valuable indication of displacement of the upper mediastinum.

The *right main bronchus* is more vertical than the left, with the result that a foreign body entering the trachea is more likely to lodge in that bronchus or one of its divisions than the left. The right main bronchus first gives off from its lateral wall the *upper lobe bronchus* and then from its anterior wall the *middle lobe bronchus*, after which it continues as the *lower lobe bronchus*. The *left main bronchus* gives off the *upper lobe bronchus* from its lateral wall and continues as the *lower lobe bronchus*. The tongue-shaped part of the left upper lobe corresponding to the middle lobe on the right side is supplied by a large branch of the left upper lobe bronchus, named the *lingular bronchus* by reason of the shape of the part of lung which it supplies. The anatomical position of these bronchi is shown diagrammatically in Figure 57.

The three lobar bronchi on the right side and the two on the left divide and subdivide like the branches of a tree (the term 'bronchial tree' is in common use) until the respiratory bronchioles are reached. Each respiratory bronchiole communicates with a cluster of alveoli, and the 'broncho-pulmonary lobule' so constituted is the basic structure of all lung tissue. The alveoli are tiny air vesicles bounded by a single layer of flattened epithelial cells which are in direct contact with the pulmonary capillaries. Exchange of the respiratory gases, oxygen and carbon dioxide, takes place between the air in the alveoli and the blood in the pulmonary capillaries.

The *right lung* differs from the left in having three lobes instead of two. The *left lung* is divided into *upper* and *lower lobes* by the *oblique fissure* which extends from the junction of the fourth or fifth rib with the vertebral column behind to the sixth costo-chondral junction in front, crossing the mid-axillary line at the level of the fifth rib. As the posterior end of the fissure is at a much higher level than its anterior end, the upper lobe, as well as being *above* the lower lobe, is also largely in front of it. It therefore follows that upper lobe lesions produce physical signs mainly on the front of the chest and lower lobe lesions on the back.

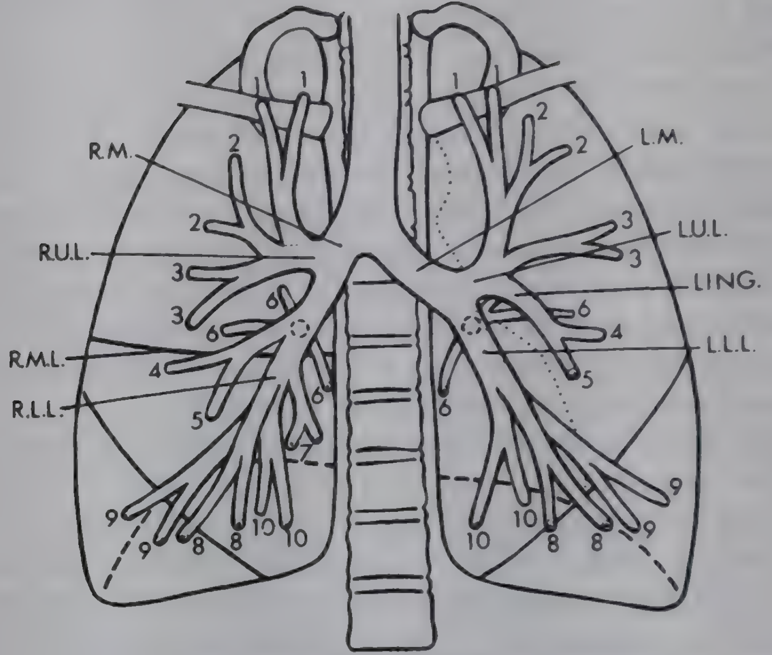
On the *right* side the oblique fissure corresponds in position to that on the left, but the lung above it is divided into *upper* and *middle lobes* by the *transverse fissure*, which runs laterally in a horizontal direction from the junction of the fourth costal cartilage with the sternum to join the oblique fissure at the level of the fifth rib in the mid-axillary line. The middle lobe is thus situated behind the lower part of the anterior chest wall.

Each lobe is composed of two or more *bronchopulmonary segments*, which represent the portions of lung tissue supplied by the main branches of each lobar bronchus.

In many diseases, e.g. pneumococcal pneumonia, collapse and lung abscess, the lesion is typically confined to a single lobe or segment. A knowledge of pulmonary anatomy, when applied to the interpretation of radiographs, may thus be of value in determining the nature of the lesion as well as its situation.

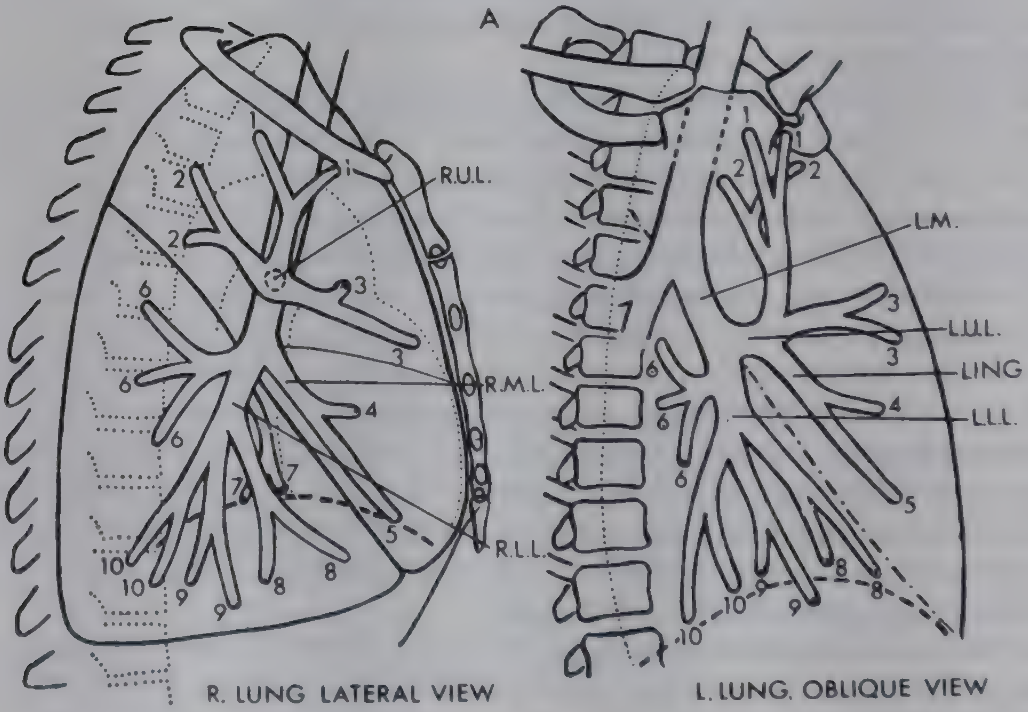
PLEURA

Each lung is closely invested with *visceral pleura*. *Parietal pleura* lines the chest wall, mediastinum and diaphragm, and is continuous with the visceral



ANTERIOR VIEW

A



R. LUNG LATERAL VIEW

L. LUNG. OBLIQUE VIEW

Fig. 57

The Anatomy of the Bronchi

A Right and Left Bronchi. B Right Bronchi. C Left Bronchi.

The oblique view of the left bronchi is shown in preference to the lateral view because at bronchography (p. 328) the right bronchi are normally outlined first and a lateral view of the left bronchi cannot then be obtained. The oblique view, which must be taken instead, has the additional advantage of showing the disposition of the left bronchi more clearly.

pleura at the pulmonary hilum. In health the two pleural layers are separated only by a thin film of lymph, but between them there is a negative (subatmospheric) pressure. This results from the natural tendency of the lung to recoil towards the hilum, a property given to it by the rich supply of elastic fibres in the bronchi, blood vessels and lung parenchyma.

If a communication develops with the atmosphere as, for example, with a penetrating wound of the chest wall or from the rupture of an emphysematous bulla, the negative intrapleural pressure draws air between the pleural layers and the potential intrapleural space becomes a real one. There is then said to be a *pneumothorax*. When the space is created by the presence of clear fluid there is said to be a *pleural effusion* or a *hydrothorax*; by pus, an *empyema*; by blood, a *haemothorax*; by both clear fluid and air, a *hydropneumothorax*; by both pus and air, a *pyopneumothorax*; and by both blood and air, a *haemopneumothorax*.

When the pleural space contains air or fluid the elastic recoil of the underlying lung is to some extent released and the lung shrinks towards the hilum, this shrinkage being referred to as *pulmonary collapse*. The larger the amount of air or fluid between the pleural layers the more marked is the degree of pulmonary collapse and the greater the impairment of function of the collapsed lung. If the quantity of air or fluid is very large it causes displacement of the mediastinum towards the opposite side, with the result that function of the opposite lung is also impaired. A gross degree of mediastinal displacement may, in addition, embarrass the action of the heart. Mediastinal displacement is recognised clinically by alteration in position of the trachea and of the cardiac apex beat.

Collapse of the lung may also occur without air or fluid in the pleural space as a result of bronchial obstruction (p. 397).

KEY TO FIG. 57

Major Bronchi

R.M.	Right main bronchus.	L.M.	Left main bronchus.
R.U.L.	Right upper lobe bronchus.	L.U.L.	Left upper lobe bronchus.
R.M.L.	Right middle lobe bronchus.	LING.	Lingular bronchus.
R.L.L.	Right lower lobe bronchus.	L.L.L.	Left lower lobe bronchus.

Segmental Bronchi[1]

Right upper lobe.	1. Apical.	2. Posterior.	3. Anterior.
Right middle lobe.	4. Lateral.	5. Medial.	
Right lower lobe.	6. Apical.	7. Medial basal (cardiac).	8. Anterior basal.
	9. Lateral basal.	10. Posterior basal.	
Left upper lobe.	1. Apical.	2. Posterior.	3. Anterior.
Lingula.	4. Superior.	5. Inferior.	
Left lower lobe.[2]	6. Apical.	8. Anterior basal.	9. Lateral basal.
	10. Posterior basal.		

---

[1] The names of the segmental bronchi are not included in the text but are given here for future reference, numbered according to international agreement.

[2] There is no medial basal bronchus on the left side.

MEDIASTINUM

The anatomy of the mediastinum has an important bearing on the diagnosis of intrathoracic disease, particularly tumours and aneurysms. These lesions are liable to involve mediastinal structures and, as a result, certain readily recognisable symptoms, physical signs and radiological abnormalities may be produced. The structures involved and the abnormality produced in each case are discussed in the section on mediastinal tumours (p. 405).

PHYSIOLOGY

Knowledge of the normal processes of respiration is of value in understanding the effects of disease of the lungs and airways, and is of great importance in therapy. Oxygen therapy, the treatment of ventilatory failure and much of the treatment of chronic bronchitis and asthma have a rational basis in applied respiratory physiology.

The aspects of the physiology of respiration which merit special attention are:

1. *Ventilation*, which includes (*a*) the mechanical processes of inspiration and expiration and (*b*) the control of ventilation at a level appropriate to metabolic needs.
2. *Perfusion* of the lungs by the output of the right heart.
3. *Distribution* of ventilation and perfusion within the lungs.
4. *Diffusion* of oxygen and carbon dioxide between the terminal airways, the alveoli and the pulmonary capillary blood.

In a typical normal adult at rest the normal pulmonary blood flow of 5 *l*/min. carries 250 ml/min. of oxygen from the lungs to the tissues and normal ventilation of about 6 *l*/min. carries 200 ml of carbon dioxide out of the body. The pressure ranges of oxygen and carbon dioxide in the arterial blood are normally closely controlled (P_{O_2} 80-95 mm Hg; P_{CO_2} 36-44 mm Hg), and observation of changes in these pressures in disease are of importance in assessing the nature and severity of any disturbance of lung function (p. 328).

Ventilation

The respiratory muscles, in ventilating the lungs, do mechanical work of two kinds, elastic and non-elastic. The first is performed against elastic forces in the lungs and chest wall which together tend to bring the chest to the position it occupies at the end of a normal expiration. Movement of the chest from this position of equilibrium involves the performance of elastic work and the storage of kinetic energy which is later available for non-elastic work during the return to the resting position. This second kind of work is largely expended in overcoming the resistance of the airways to the inspiratory and expiratory flow of air and to a smaller extent in displacing soft and inelastic tissues.

During quiet breathing inspiration is 'active' and expiration 'passive'. Inspiration against abnormal resistance (whether elastic or non-elastic) may bring accessory muscles such as the sternomastoids and scaleni into play; expiration, if forced or performed against abnormal airway resistance, is accomplished with the aid of the accessory muscles of expiration, chiefly those of the abdominal wall.

Elastic work is increased when the lungs are made more rigid (less compliant) by pulmonary oedema or fibrosis or when the chest wall is made more unyielding by ankylosing spondylitis or severe kyphoscoliosis. Rapid shallow breathing is often observed in these conditions. Non-elastic work is increased by rapid breathing and by conditions causing airway obstruction such as asthma, chronic bronchitis, emphysema and tumours of major bronchi. The metabolic cost of breathing is normally low: an increase in ventilation of 1 *l*/min. raises oxygen uptake by about 1 ml/min. at most. In disease, this figure may rise to as much as 10 ml oxygen per min. per *l*/min. increase in ventilation. Under such circumstances breathing accounts for an important fraction of metabolic oxygen uptake.

Not all the volume of the inspired ventilation takes part in gas exchange in the lungs. Some of each breath ventilates the conducting airways down to the respiratory bronchioles, which constitute the 'anatomical' dead space; because of maldistribution (see below) some of each breath is wasted in ventilating underperfused parts of the lungs. The proportion of wasted ventilation in each breath (physiological dead space: tidal volume ratio, Vd/Vt) is normally one-fifth to one-third, but may be much increased, sometimes to as much as two-thirds, in disease. The volume which remains takes part in gas exchange and constitutes the alveolar ventilation, which is normally about 5 *l*/min. at rest. It follows that if the proportion of wasted ventilation is greater than normal a greater total ventilation is needed to achieve normal alveolar ventilation.

Normally, alveolar ventilation is closely matched to the excretion of carbon dioxide and this matching is reflected in a normal level of arterial $P\text{CO}_2$. If alveolar ventilation is reduced in proportion to carbon dioxide excretion, the arterial $P\text{CO}_2$ must rise (hypercapnia), and if alveolar ventilation becomes excessive, the arterial $P\text{CO}_2$ will fall (hypocapnia). Indeed, the arterial $P\text{CO}_2$ reflects alveolar ventilation and the production of carbon dioxide just as the blood urea concentration reflects renal urea clearance and the metabolic production of urea.

Generalised alveolar underventilation is most commonly found as a late result of chronic bronchitis and emphysema. It also occurs if respiration is depressed by narcotics, anaesthetics or intracranial disease. It may ensue when the respiratory muscles are paralysed or when gross deformity of the chest wall limits thoracic or diaphragmatic movement, as in kyphoscoliosis. Lowering of the arterial $P\text{O}_2$ (hypoxaemia) is an inevitable result of alveolar underventilation when air is breathed. Giving oxygen will correct this, but the hypercapnia is corrected only when alveolar ventilation is improved.

Alveolar overventilation occurs in asthma of mild or moderate severity, in interstitial lung disease, in pulmonary vascular disease (e.g. pulmonary embolism), in salicylate overdosage, as a result of pontine lesions, or from anxiety or hysteria. It is often a prominent manifestation of metabolic acidosis (p. 201).

Control of Breathing

Rhythmical discharges originating in the reticular substance of the brain stem provide the basis for co-ordinated respiratory movements; it is convenient to use the term 'respiratory centre' for the neurones involved in breathing, but the distribution and organisation of these neurones is highly complex. Normal breathing is modified by afferent impulses from many sources, which are best considered in two groups:

1. Those arising within the central nervous system and from receptors other than chemoreceptors ('neural stimuli').
2. Those arising from chemoreceptors sensitive to the composition of blood or cerebrospinal fluid ('chemical stimuli').

Afferent impulses of the first group mediate (*a*) the changes in rate and depth of breathing which may be consciously induced for short periods, (*b*) the central neurogenic hyperventilation which occurs in certain lesions of the pons and midbrain, (*c*) the respiratory depression associated with medullary compression and (*d*) the respiratory stimulation which originates in limb receptors, as in exercise. These impulses arise from receptors in muscles and joints in the chest wall, and from pulmonary receptors sensitive to stretch, bronchial irritation and pulmonary capillary distension. Pulmonary inflation and deflation (Hering-Breuer) reflexes are present in the newborn, but are weak in adults except under general anaesthesia.

The second group of afferent impulses arises in chemosensitive cells located in the carotid and aortic bodies (peripheral chemoreceptors) and intracranially (central chemoreceptors). In animals central chemosensitive areas are located on the ventro-lateral surface of the medulla, but in man their situation is uncertain.

Ventilation is increased when the peripheral chemoreceptors are stimulated by arterial hypoxia; at rest, the stimulus is not strong unless arterial Po_2 is below 60 mm Hg, and becomes powerful at about 30 mm Hg. The peripheral chemoreceptors are also stimulated by an increase in the hydrogen-ion activity of arterial blood. Central chemoreceptors are stimulated by an increase in the hydrogen-ion activity of cerebrospinal fluid (CSF). A rise in Pco_2 of the arterial blood is accompanied by increasing acidity of both blood and CSF and therefore stimulates both central and peripheral chemoreceptors. For this reason, inhalation of carbon dioxide is one of the strongest known respiratory stimulants. In the presence of mild or moderate hypoxia its effect is increased, but severe hypoxia acts as a central depressant, as in asphyxia. Pyrexia increases the sensitivity of the respiratory centre; all sedative drugs, particularly opiates, depress it.

In some patients with chronic bronchitis the normal sensitivity to increased arterial Pco_2 is greatly reduced. In such patients chronic alveolar underventilation occurs and relief of the concurrent hypoxaemia may, by removing one of the remaining stimuli to breathing, be followed by worsening of the hypercapnia.

Distribution of Gas and Blood in the Lungs

Gas exchange in the lungs is inefficient unless alveolar ventilation is distributed uniformly to different parts of the lungs and is matched by uniform distribution of blood flow. The composition of blood leaving an individual alveolus depends on the composition of the mixed venous blood entering the pulmonary capillaries and the ratio between the ventilation of and blood flow around the alveolus. The possible values of this ventilation: perfusion ratio ($\dot{V}\text{A}/\dot{Q}$) lie between infinity (ventilation but no perfusion) and zero (perfusion but no ventilation). Thus areas of lung with $\dot{V}\text{A}/\dot{Q} = \infty$ behave as dead space, giving rise to wasted ventilation, while areas with $\dot{V}\text{A}/\dot{Q} = 0$ behave as a physiological right-to-left shunt or venous admixture effect, giving rise to wasted perfusion.

The number of alveoli in the lung and the possible range of ventilation: perfusion ratios is so large that it has become conventional to treat the lungs *as if* they were made up of three compartments:

(*a*) a compartment normally ventilated and perfused,
(*b*) physiological dead space, contributed to by all alveoli whose $\dot{V}\text{A}/\dot{Q}$ exceeds unity, and including the anatomical dead space,
(*c*) physiological shunt, contributed to by all alveoli with $\dot{V}\text{A}/\dot{Q}$ less than unity, and including the small anatomical or 'true' right-to-left shunts through such pathways as bronchial-pulmonary venous anastomoses.

It follows that if the range of ventilation: perfusion ratios found in the lungs is wider than normal the physiological dead space and physiological shunt will be larger than normal and gas exchange will become less efficient.

Even in the normal lung, distribution of ventilation and perfusion is imperfect. In the erect posture, gravity favours the distribution of blood flow to the bases of the lungs and of ventilation to the upper zones. In most forms of lung disease, distribution of ventilation and perfusion is further impaired, and it is easy to visualise how pathological mechanisms may have this effect. For example, ventilation may be impaired by

(*a*) bronchial or bronchiolar obstruction (tumour, secretions, mucosal oedema, bronchoconstriction),
(*b*) destruction of elastic tissue (as in emphysema),
(*c*) pulmonary collapse, consolidation, fibrosis or oedema,
(*d*) chest wall deformities.

Blood flow is reduced or abolished by pulmonary embolism or thrombosis or by obliteration of areas of the pulmonary capillary bed by necrosis or fibrosis.

The consequences of maldistribution are twofold. First, as has been shown above, an increase in physiological dead space means that a greater total ventilation is needed to achieve a given alveolar ventilation. Secondly, any increase in physiological shunt causes arterial hypoxaemia. Any tendency to hypercapnia due to perfusion of alveoli with low $\dot{V}\text{A}/\dot{Q}$ ratios can be compensated for by overventilation of alveoli with high $\dot{V}\text{A}/\dot{Q}$ ratios. This preserves a normal or low arterial $P\text{CO}_2$, but the arterial hypoxaemia is little affected. Maldistribution, with areas of low $\dot{V}\text{A}/\dot{Q}$ ratio, is therefore the most important single cause of hypoxaemia in disease, and is found in a wide variety of conditions. Fortunately, administration of oxygen raises the alveolar Po_2, even in poorly ventilated alveoli, and corrects the hypoxaemia.

Diffusion of Gases in the Lungs

Oxygen and carbon dioxide are exchanged across the alveolar membrane by diffusion from a site of higher to one of lower partial pressure. It might be expected that if the alveolar wall became thickened, as in so-called interstitial lung disease, diffusion of gases, particularly of oxygen, would be impaired. However, most conditions which might be expected to have this effect can also give rise to maldistribution of ventilation and blood flow, and analysis suggests that the effect on distribution is usually the chief cause of hypoxaemia in these conditions.

If the area available for gas exchange is reduced (e.g. in emphysema) or if, because of maldistribution, the effective area is reduced, the ability of the lung to transfer gases will also diminish. Such a reduction may not be significant at rest, but may limit the amount of oxygen which can be taken up during exercise and may become a cause of hypoxaemia under these circumstances. It can be corrected by administration of oxygen.

The overall ability of the lung to transfer gases can be readily measured by relating the uptake of carbon monoxide to the alveolar CO pressure when a very weak mixture of this gas is breathed. By this method, values for *gas transfer factor* or *diffusing capacity* of the lung are obtained. The name *gas transfer factor* is preferable, since 'diffusing capacity' carries the implication that diffusion itself is being measured, whereas in fact the measurement is affected by other factors, such as maldistribution.

COMMON MANIFESTATIONS OF RESPIRATORY DISEASE

1. **Cough.** Cough is the most frequent of all respiratory symptoms. It may be short, painful and half-suppressed, as when dry pleurisy accompanies pneumonia. It may be loose and readily productive of sputum as in bronchiectasis, or paroxysmal, ineffectual and exhausting, as in some cases of chronic bronchitis and asthma. It is usually an early symptom in bronchial carcinoma but may be a relatively late development in pulmonary tuberculosis. Generally it is worse at night or on waking. Often it is aggravated by changes in temperature or weather. The explosive character of a normal cough is lost when laryngeal paralysis is present ('bovine cough'). Cough is accompanied by stridor (p. 322) in whooping-cough and in the presence of laryngeal or tracheal obstruction.

2. **Sputum.** Purulent sputum is due to bacterial infection in the respiratory tract and is typically seen in acute bronchitis, infective exacerbations of chronic bronchitis, bacterial pneumonia, bronchiectasis and lung abscess. In the last two conditions the sputum may be copious and is sometimes foetid. Mucoid sputum is due to oversecretion of bronchial mucus. It is frequently present in chronic

bronchitis and bronchial asthma. In early cases of pulmonary tuberculosis the sputum is mucoid but in advanced cases it is usually purulent.

3. **Haemoptysis.** Haemoptysis of all grades of severity may occur, from slight streaking of the sputum with blood, which is a common symptom in acute and chronic bronchitis, to a massive haemorrhage. Frank haemoptysis, however small, must always be regarded as of potentially serious significance and demands the fullest investigation. Bronchial carcinoma, pulmonary infarction, bronchiectasis, pulmonary tuberculosis and mitral stenosis are the most common causes.

4. **Chest Pain.** Broadly speaking there are two types of chest pain associated with respiratory disease:

(*a*) Central retrosternal pain of a sore, 'scratchy' character made worse by coughing, but not by deep breathing, and usually caused by inflammation of the trachea (tracheitis).

(*b*) Lateral chest pain, usually in the pectoral or axillary regions but sometimes in the back, of a sharp, stabbing character, made worse by deep breathing and coughing, and caused by inflammation of the pleura.

The second type of pain, which is referred to as *pleural* pain, is of greater clinical importance than the first and is a common symptom in respiratory disease. The pain is thought to be due to stretching of the inflamed parietal pleura (the visceral pleura is insensitive to painful stimuli) and, as would be expected, it is maximal at the end of inspiration. Patients with pleural pain try to minimise it by taking shallow breaths and by suppressing cough as much as possible. The pain is referred to the area of skin supplied by the same spinal nerves as those supplying the inflamed area of pleura. Usually it is referred to the chest wall, but when the pleura lining the diaphragm is inflamed it may be referred to the cutaneous distribution of the supraclavicular nerves which have the same spinal roots (third and fourth cervical) as the phrenic nerve. Pain in the front and top of the shoulder is thus characteristic of *diaphragmatic pleurisy*. Pleural pain may also be referred to the anterior abdominal wall, where it may be difficult to distinguish from the pain of an acute abdominal emergency.

The *pleural rub*, which is a common physical sign in dry pleurisy, is due to the rubbing together of pleural surfaces roughened by fibrinous exudate.

The effusion of fluid between the layers of the pleura diminishes pain by reducing the movement of the chest wall and abolishes the pleural rub by separating the pleural surfaces.

5. **Dyspnoea.** It has been said that breathing is the only involuntary act which is carried out by voluntary muscle, and this is normally so. Dyspnoea is the subjective state in which the effort of breathing reaches consciousness, usually under circumstances in which a normal person would not be aware of his breathing at all. It should be distinguished from hyperpnoea, where the volume of ventilation is increased, but no abnormal sensation is felt, and tachypnoea, an excessive respiratory rate.

Dyspnoea occurs as a symptom in a wide variety of diseases, and no single theory can adequately explain why it occurs. In conditions where airway resistance is high, such as asthma or chronic bronchitis, the increased mechanical work needed to achieve a given volume of ventilation may account for it. A similar explanation may be given for the dyspnoea of diseases causing lung stiffness, such as fibrosing alveolitis (p. 407), with the added factor that the hypoxaemia which occurs readily during exercise in such diseases may still further increase the drive to breathe. This explanation is less satisfactory for the dyspnoea of heart disease, and still less so for the dyspnoea found in anaemia, where both the lungs and the arterial oxygen pressure are normal. It has been suggested that the sensation arises from 'inappropriateness' between the amount of breathing which the patient feels is needed for a given task and the amount he has in fact to produce—a feeling comparable to that experienced when picking up what seems to be an ordinary rubber ball and finding it is filled with lead. This throws some light on the nature of the sensation, but still leaves its cause obscure.

In mild heart or lung disease, dyspnoea is noticeable only on effort, and the presence of dyspnoea at rest is an indication that the disease is severe or advanced. In conditions such as chronic bronchitis, much of the respiratory reserve may have been lost before a sedentary patient complains of dyspnoea, and measurements of ventilatory capacity show that irreversible airway obstruction is already established. Complaints of dyspnoea should therefore be taken seriously, for although the symptom is commonly found in anxiety states, it also may occur early in diseases such as pulmonary thrombo-embolism or interstitial lung disease at a stage when abnormalities may not be apparent clinically or radiologically. Tests of pulmonary function and objective assessment of exercise capacity are then of value.

6. **Wheeze.** In all forms of generalised obstructive airway disease, particularly bronchial asthma, wheeze is usually a conspicuous symptom. It is a musical sound heard best during expiration, and is associated with numerous rhonchi on auscultation. *Stridor*, on the other hand, occurs when one of the major airways (larynx, trachea or main bronchus) is obstructed. It is a crowing sound heard best during inspiration, and is associated with a persistent low-pitched rhonchus audible all over the chest.

7. **Hypoxaemia.** Hypoxaemia is present if either the pressure or content of oxygen in arterial blood is reduced, and if severe enough may result in visible central cyanosis. The normal arterial Po_2 is over 90 mm Hg at the age of 20, and falls to around 80 mm Hg at 60. Above this age a further fall in Po_2 of up to 10 mm Hg occurs on recumbency because of closure of airways in the dependent regions of the lungs. The most frequent and important cause of hypoxaemia in respiratory disease is the presence in the lungs of areas where the distribution of ventilation and perfusion is disturbed and ventilation is low in relation to perfusion. Hypoxaemia also inevitably results from alveolar underventilation or if an atmosphere poor in oxygen is breathed, as at high altitudes. Impairment of diffusion across the alveolar wall may cause hypoxaemia during exercise, but is hardly ever an important factor at rest. The hypoxaemia due to all these causes is reversed by giving oxygen (p. 330). Hypoxaemia due to congenital heart disease (p. 295) or vascular anomalies, with shunting of blood from the right to the left of the circulation past the lungs, is never entirely

reversed by oxygen. Hypoxaemia also occurs if the oxygen capacity of the blood is reduced, as in anaemia or carbon monoxide poisoning.

8. **Hypercapnia.** Hypercapnia is present if the pressure of carbon dioxide in the arterial blood ($Paco_2$) exceeds the normal limits (36-44 mm Hg at rest). Clinically significant hypercapnia occurs when the $Paco_2$ exceeds 50 mm Hg. As has been seen (p. 317), the finding of a raised $Paco_2$ implies that alveolar ventilation is inadequate in relation to the carbon dioxide production of the body; the causes of hypercapnia are therefore those of alveolar underventilation. Alveoli in which the ventilation: perfusion ratio is low also contribute to hypercapnia.

The finding of hypercapnia implies either that the normal sensitivity of the respiratory centre to carbon dioxide has been reduced, or that mechanical limitation prevents a normally responsive centre from maintaining adequate alveolar ventilation.

Clinical features suggestive of hypercapnia include peripheral vasodilatation, with warm extremities and bounding pulses, sweating, muscle twitching, headache, drowsiness, coma, retinal venous distension and, rarely, papilloedema. Unfortunately, none of these signs is specific and the diagnosis must be made by measurement of the pressure of carbon dioxide in arterial or mixed venous blood.

Hypercapnia has three consequences of clinical importance: (*a*) it aggravates hypoxaemia by lowering the pressure of oxygen in the alveolar air, (*b*) when acute, it reduces the arterial pH (respiratory acidosis), although renal retention of bicarbonate tends to compensate for this over a period of hours or days (p. 381), and (*c*) when of a severe degree ($Paco_2 > 80$ mm Hg), it induces drowsiness, which may proceed to coma.

9. **Respiratory Failure.** Respiratory failure is said to occur when the normal pressures of oxygen and carbon dioxide in the blood are no longer maintained. For practical purposes, this means the finding of either a Pao_2 of less than 60 mm Hg or a $Paco_2$ of more than 50 mm Hg.

It follows that two varieties of respiratory failure can be recognised. In the first $Paco_2$ is normal or low, but Pao_2 is reduced. The second, in which the $Paco_2$ is elevated and the Pao_2 is reduced, is often termed 'ventilatory failure'. The mechanisms responsible for the hypoxaemia in each type have already been discussed (p. 317), but it must be stressed once more that the finding of hypercapnia means that the normal mechanisms controlling breathing have been upset.

The causes of respiratory failure of the first type are many, and include any of the pathological causes of maldistribution of ventilation and perfusion in the lungs (p. 319). Among the most important are bronchial asthma, pneumonia, pulmonary collapse, pulmonary oedema, fibrosing and allergic alveolitis, myocardial infarction and shock.

The most common pulmonary cause of ventilatory failure is chronic bronchitis, particularly when complicated by acute respiratory infection. Other causes include respiratory paralysis (p. 876), deformities of the chest such as severe kyphoscoliosis, and depression of the respiratory centre, particularly by narcotic or sedative drugs.

The treatment of respiratory failure of the first type, in which hypoxaemia is not accompanied by hypercapnia, must always include oxygen, which can be given without strict control of the inspired concentration. In addition, treatment appropriate to the particular cause of the failure must be given. Treatment of the second type is discussed on page 322.

10. **Clubbing of the Fingers and Toes.** The cause of clubbing, which is most readily recognised in the fingers, is not known but it is frequently found in patients with certain types of respiratory disease, notably lung cancer and chronic intrathoracic suppuration such as bronchiectasis, lung abscess and empyema. It does not occur in chronic bronchitis or emphysema unless there is accompanying pulmonary suppuration or if the patient has developed a tumour, nor in pulmonary tuberculosis except in advanced cases.

Clubbing also occurs in certain other conditions. It is usually present in subacute bacterial endocarditis and cyanotic congenital heart disease; it is found occasionally in Crohn's disease, malabsorption syndrome and cirrhosis of the liver, and rarely in healthy subjects as a familial trait. The earliest indication of finger clubbing is an abnormal degree of fluctuation at the bases of the nails. With more advanced clubbing there is, in addition, an increase in the curvature of the nails and bulbous swelling of the finger tips.

THE INVESTIGATION OF RESPIRATORY DISEASE

In most respiratory diseases a reasonably accurate diagnosis can be made from the history and physical examination alone, but in several important conditions, notably pulmonary tuberculosis and bronchial carcinoma, these methods are inadequate and the diagnosis can be confirmed or excluded only by more specialised procedures such as radiological, bacteriological or endoscopic examination. In taking the history, particular enquiry must always be made about symptoms such as cough, sputum, haemoptysis, pain, breathlessness, wheeze and nasal discharge. The patient must also be asked about any previous respiratory illness, about any family history of tuberculosis and about a history of occupational exposure to dust.

Physical Examination

Before the chest itself is examined the temperature should be taken, and a note made of the rate and character of breathing, the type and severity of any cough and the amount and character of the sputum. In addition, particular care must be taken to determine whether or not there is cyanosis, clubbing of the fingers or enlargement of the supraclavicular lymph nodes, these features being of special significance in respiratory disease.

The upper respiratory tract should be examined next, with particular regard to nasal discharge or obstruction, oral sepsis, and infection or enlargement of the tonsils. The presence of hoarseness or a 'bovine' cough would draw attention to the need for laryngoscopic examination (p. 328). The chest wall should then be carefully inspected for soft tissue abnormalities such as cutaneous lesions, subcutaneous swellings (including lumps in the breast) and bulging or indrawing of intercostal spaces, and for skeletal abnormalities such as an increase of the antero-posterior diameter of the chest relative to its lateral diameter. The position of the trachea and of the apex beat should be noted and the chest expansion measured. Rib movement, vocal fremitus and the percussion note should always be compared in equivalent positions on the two sides of the chest. The terms used to describe the various types of percussion note are: hyper-resonant, normal, impaired, dull and stony dull. At auscultation, attention should be directed in turn to the breath sounds, added sounds and vocal resonance.

Breath Sounds

The following terms are used: vesicular, vesicular with prolonged expiration, diminished vesicular, absent breath sounds, high-pitched bronchial ('tubular'), low-pitched bronchial ('cavernous' or 'amphoric') breath sounds.

Added Sounds

(i) *Rhonchi* are produced by narrowing of the lumen of the bronchi by spasm of bronchial muscle, swelling of bronchial mucosa or tenacious exudate adherent to bronchial walls. Rhonchi may be high-pitched, medium-pitched or low-pitched, according to the size of the bronchi in which the sounds are produced.

(ii) *Crepitations* are usually produced by secretion lying within alveoli, bronchi or pulmonary cavities. They may be fine, medium or coarse in quality, and may either disappear or become more numerous after coughing. Crackling crepitations, unaltered by coughing, are a feature of interstitial lung disease (p. 407).

(iii) *Pleural rub* is a diagnostic sign of pleural inflammation. It is a grating or creaking sound, unaltered by coughing, audible during both inspiration and expiration.

Vocal Resonance

The following terms are used: normal, increased, diminished or absent vocal resonance, aegophony, whispering pectoriloquy.

THE INTERPRETATION OF PHYSICAL SIGNS

Certain groups of physical signs are typically associated with certain pathological changes in the lungs and pleura. Such changes are not necessarily specific for one particular disease. For example, consolidation may occur in pneumonia or tuberculosis, and fluid may be present in the pleural space in tuberculous pleurisy, empyema or congestive cardiac failure. Each group of physical signs should therefore be correlated with the gross pathological lesion by which the signs are produced rather than with any specific disease, the diagnosis of which depends on an analysis of all the clinical and other evidence.

The characteristic physical signs of the more common lesions are shown on Table 4.

TABLE 4

Summary of Typical Physical Signs in the More Common Respiratory Diseases

Pathological Process	*Movement of Chest Wall*	*Mediastinal Displacement*	*Percussion Note*	*Breath Sounds*	*Vocal Resonance*	*Accompa ments*
Consolidation: as in lobar pneumonia	Reduced on side affected	None	Dull	High-pitched bronchial	Increased (with aegophony) Whispering pectoriloquy	Fine crepit tions earl Coarse crep tations lat
Collapse due to obstruction of major bronchus	Reduced on side affected	Towards lesion	Dull	Diminished or absent	Reduced or absent	None
Collapse due to peripheral bronchial obstruction	Reduced on side affected	Towards lesion	Dull	High-pitched bronchial	Increased (with aegophony) Whispering pectoriloquy	None earl coarse cre tations la
Localised fibrosis and/or bronchiectasis	Slightly reduced on side affected	Towards lesion	Impaired	Low-pitched bronchial	Increased	Coarse crepitatio
Cavitation (typical signs only when cavity is large and linked with bronchus)	Slightly reduced on side affected	None, or towards lesion	Impaired	'Amphoric' bronchial	Increased Whispering pectoriloquy	Coarse crepitatio
Pleural effusion Empyema	Reduced or absent (depending on size) on side affected	Towards opposite side	Stony dull	Diminished or absent (occasionally high-pitched bronchial)	Reduced or absent (occasionally increased with aegophony)	Pleural ru some case (above effusion)
Pneumothorax	Reduced or absent (depending on size) on side affected	Towards opposite side	Normal or hyper-resonant	Dimished or absent (occasionally faint high-pitched bronchial)	Reduced or absent	Tinkling crepitatio when flui present
Bronchitis: Acute Chronic	Normal or symmetrically diminished	None	Normal	Vesicular with prolonged expiration	Normal	Rhonchi, usually wi some coa crepitatio
Bronchial asthma	Symmetrically diminished	None	Normal	Vesicular with prolonged expiration	Normal or diminished	Rhonchi, mainly ex piratory a high-pitch
Diffuse lobular pneumonia	Symmetrically diminished	None	May be impaired	Usually harsh vesicular with prolonged expiration	Normal	Rhonchi a coarse crepitatio
Diffuse pulmonary emphysema	Symmetrically diminished	None	Normal	Diminished vesicular with prolonged expiration	Normal or reduced	Rhonchi ar coarse cre tations fr associated bronchitis
Interstitial lung disease	Symmetrically diminished	None	Normal	Harsh vesicular with prolonged expiration	Usually increased	Crackling crepitatio uninfluenc by coughi

(From *Clinical Examination*, 3rd ed. 1973. Macleod, J. Edinburgh and Lond
Churchill Livingstone.)

SPECIAL METHODS OF INVESTIGATION

1. **Radiological Examination of the Chest.** Although radiological examination of the chest is now widely employed as a primary diagnostic measure ('mass radiography') it should not be regarded as a short-cut to diagnosis. It may, however, provide:

(*a*) Evidence of a lesion within the thorax too small to be detected by physical examination or which because of its nature or situation does not give rise to abnormal physical signs, e.g. early tuberculosis or tumour.

(*b*) A more accurate assessment of the size and position of pulmonary, pleural and mediastinal lesions than can be obtained from physical examination. Lateral as well as postero-anterior radiographs are necessary for this purpose.

(*c*) More accurate information about the nature of the lesions than can be obtained from physical examination. *Tomography* is of particular value in this respect as it provides better definition of intrathoracic lesions, and facilitates the recognition of features such as cavitation, calcification and bronchial obstruction.

(*d*) Accurate information regarding the size, shape and position of the heart.

(*e*) Information regarding the position and function of the diaphragm, which can be observed radiologically by the technique of radioscopy (p. 223).

(*f*) Evidence of disease or injury affecting the bony structures of the thorax.

It is important to remember that in some diseases, such as bronchitis and asthma, the chest radiograph may be normal.

2. **Bacteriological and Cytological Examination**

(*a*) SPUTUM. Bacteriological examination of the sputum seldom provides conclusive diagnostic information except when tubercle bacilli are isolated. The findings in other circumstances must be interpreted in conjunction with the results of clinical and, if necessary, radiological examination.

Cytological examination, by demonstrating cancer cells in the sputum, may enable a diagnosis of bronchial carcinoma to be made.

(*b*) PLEURAL FLUID. This should always be examined cytologically and bacteriologically. A special search should be made for tubercle bacilli if the fluid is serous and for pyogenic organisms and tubercle bacilli if it is purulent. When malignant disease is suspected, especially if the fluid is blood-stained, it should also be examined histologically for cancer cells.

3. **Serological Examination.** This may be of value in the diagnosis of virus infections (p. 337) and some allergic disorders (p. 382).

4. **Haematological Examination.** Estimation of the total and differential leucocyte count may help to distinguish pyogenic infection from tuberculous or virus infection.

5. **Skin Tests.** The tuberculin test (p. 360) and Kveim test (p. 410) may be of value in the diagnosis of tuberculosis and sarcoidosis respectively. Prick tests (p. 378) are useful in the investigation of allergic diseases.

6. **Laryngoscopy**. The larynx is inspected either by means of a mirror placed in front of the uvula (*indirect* laryngoscopy) or through an illuminated metal tube (*direct* laryngoscopy).

7. **Bronchoscopy**. The trachea and larger bronchi are inspected by means of an illuminated metal tube, through which tissue can be removed for histological examination (bronchial biopsy). The normal range of bronchoscopic vision extends to the origins of all segmental bronchi (Fig. 57, p. 314).

8. **Bronchography** (p. 403). The bronchi are outlined by contrast medium instilled into the trachea, and chest radiographs (bronchograms) are then taken.

9. **Lymph Node Biopsy.** Histological examination of an enlarged lymph node removed from the neck or axilla, or from the mediastinum by the technique of mediastinoscopy, may provide a firm diagnosis in conditions such as bronchial carcinoma, tuberculosis, reticulosis and sarcoidosis.

10. **Pleural Biopsy.** In patients with pleural effusion it is possible to obtain a specimen of parietal pleura suitable for histological examination by means of Abrams' pleural biopsy 'punch'. This procedure is simple and safe, and may be of considerable value in determining the cause of a pleural effusion.

If it is unsuccessful, the pleural surfaces can be inspected with a thoracoscope inserted through an intercostal space, and if a pleural lesion is seen, a biopsy can be performed under visual control.

11. **Lung Biopsy.** When a diagnosis cannot be made in any other way it may be necessary to obtain a specimen of lung tissue for histological examination either by formal thoracotomy or by drill biopsy through the chest wall.

12. **Tests of Pulmonary Function.** Many of the procedures mentioned above are of great assistance in arriving at a pathological diagnosis, but investigations of a different type are necessary to determine the effects of disease on pulmonary function and to assess the response to therapy (p. 379). Disturbances of the mechanical properties of the lungs, of ventilation, of control of breathing, of the distribution of ventilation and perfusion within the lungs and of diffusing capacity can all be measured. Some of the tests require a high degree of skill and elaborate apparatus, but others are simple routine procedures which can be undertaken by any doctor without special training.

(*a*) ESTIMATION OF VENTILATORY CAPACITY. The patient is asked to take in as deep a breath as possible and then expel it as hard and as fast as possible. If the forced expiration is made into a recording spirometer of low resistance and low inertia, the *forced expiratory volume* in the standard time of 1 second (FEV_1) can be measured; if the forced expiration is continued till no more gas can be expelled, the *forced vital capacity* (FVC) is measured. The ratio of these two volumes may be expressed as a percentage (FEV/FVC %); normal people can expel between 80 and 65 per cent of the FVC in 1 second, depending on age and sex.

In diseases which cause narrowing of the airways during expiration, such as asthma and chronic bronchitis, the FEV/FVC % is reduced, sometimes to 40 per cent or less. This is due to a greater reduction in FEV than in FVC, and this type of ventilation defect is called '*obstructive*'. In diseases such as interstitial lung disease or ankylosing spondylitis, which make the lungs and chest wall more rigid, FEV and FVC are reduced in the same proportion and FEV/FVC % is normal, as the airways are relatively unaffected. This type of defect is called '*restrictive*'. Discovery of airway obstruction is an indication to repeat the spirometric measurements after a bronchodilator drug (p. 379) has been given; reversibility of airway obstruction is found in asthma and in some patients with chronic bronchitis.

During forced expiration, the *peak expiratory flow rate* (PEFR) can be measured by apparatus which is simpler and cheaper than the average spirometer. PEFR is reduced in conditions causing airway obstruction, and is a good indicator of the severity of the obstruction. The measurement has therefore become popular in clinical practice because of its speed and simplicity. PEFR is little affected by conditions causing a restrictive type of ventilatory defect, and is therefore of no value in diagnosing or assessing them.

Even if no apparatus other than a watch and stethoscope is available, forced expiration can still be used to assess ventilatory capacity. Normal people can empty their chest from full inspiration in 4 seconds or less. Prolongation of the *forced expiratory time* (FET) to more than 6 seconds indicates airway obstruction and a reduction in FEV/FVC % to less than 50 per cent. The end-point of FET is detected by placing the chest-piece of a stethoscope over the trachea in the suprasternal notch.

(*b*) ANALYSIS OF ARTERIAL BLOOD. Apparatus for arterial blood-gas analysis is now available in most hospitals, but the estimations require skill. Knowledge of the Pa_{CO_2} provides the answer to the question, 'Is the patient breathing enough?', and is of particular value in the management of ventilatory failure (p. 332). Measurement of the partial pressure of carbon dioxide in mixed venous blood ($P\bar{v}_{CO_2}$) by the rebreathing method is a satisfactory alternative when blood-gas estimations cannot be undertaken. If the arterial pH and Pa_{CO_2} or $P\bar{v}_{CO_2}$ are known, it is often possible to deduce the type of any disturbance of acid: base balance (p. 204) which may be present. Knowledge of the Pa_{O_2} or arterial oxygen saturation allows accurate assessment of hypoxaemia (p. 322) and of the effects of oxygen therapy (p. 331).

These simple measurements are thus of value in distinguishing between some types of respiratory disorder, as well as in providing an index of their severity. Serial measurements are valuable in following changes in pulmonary function, whether occurring spontaneously or in response to treatment.

THE TREATMENT OF RESPIRATORY DISEASE

Infection

1. **Bacterial Infection.** The chemotherapy of bacterial infection of the bronchi, lungs and pleura will be described in the sections on individual diseases. Certain general principles are, however, applicable to all cases.

Before any treatment is started a specimen of sputum, a laryngeal swab (if there is no sputum) or a specimen of pleural fluid should be sent for bacteriological examination.

In acute bacterial infections it is usually necessary to begin chemotherapy before the results of bacteriological examination are available. The choice of antibiotic in these circumstances is based on clinical impressions of the nature and severity of the illness.

If a clinical diagnosis of acute bronchitis, pneumonia or empyema is made and the patient is not seriously ill, treatment should be started with penicillin, to which most infections of this type respond. When the acute infection is a complication of chronic bronchitis, asthma or bronchiectasis, one of the broad-spectrum antibiotics should be preferred. If the patient is gravely ill and there is any reason to suspect infection with *Staph. pyogenes*, an antibiotic to which that organism is unlikely to be resistant, e.g. cloxacillin or sodium fusidate, must be given.

As soon as the results of bacteriological examination and sensitivity tests are received, appropriate modifications in antibiotic therapy can be made, if necessary.

Factors which interfere with the response to antibiotics must be corrected, e.g. an empyema must be aspirated or drained and bronchiectatic cavities and lung abscesses must be kept dry by postural drainage.

2. **Virus Infection.** The viruses which infect the respiratory tract are uninfluenced by chemotherapy, but secondary bacterial infection, which occurs in many cases, often requires treatment with an appropriate antibiotic. Infection caused by small bacteria, such as coxiella, mycoplasma and chlamydia, usually responds to tetracycline.

3. **Fungal Infection.** The treatment of respiratory diseases caused by fungi is described on page 373.

Oxygen Therapy

Oxygen is present in the air at a concentration of 21 per cent and at sea level the pressure of oxygen in inspired tracheal air is almost 150 mm Hg. Arterial blood of normal haemoglobin concentration contains about 20 ml oxygen per 100 ml; at a Pa_{O_2} of 100 mm Hg, 0·3 ml oxygen per 100 ml is dissolved in the plasma and the rest is bound to haemoglobin.

Therapeutic Indications. The objectives of oxygen therapy are (1) to overcome the reduced pressure and quantity of oxygen in the blood found in hypoxaemia, and (2) to increase the quantity of oxygen carried in solution in the plasma even when the haemoglobin is fully saturated. The causes of hypoxaemia have already been discussed (p. 322). Raising the alveolar P_{O_2} by administration of oxygen overcomes the hypoxaemia consequent upon a high alveolar P_{CO_2}; when the oxygen pressure is raised in alveoli which are poorly ventilated but perfused, the blood perfusing them becomes fully saturated and the hypoxaemia due to maldistribution of ventilation and perfusion is overcome. A raised alveolar P_{O_2} will also correct hypoxaemia due to limitation of diffusing capacity.

The cause of hypoxaemia least susceptible to oxygen therapy is right-to-left shunting, either through circulatory channels by-passing the lungs, or through parts of the lungs in which the alveoli are completely unventilated and thus inaccessible to inspired oxygen. The increased amounts of dissolved oxygen carried by blood which has perfused alveoli with a high Po_2 can saturate the haemoglobin in small quantities of shunted blood; persistence of cyanosis when pure oxygen is breathed indicates that the shunt is larger than 20 per cent of the cardiac output. This accounts for the observation that the cyanosis of congenital heart disease is not relieved by oxygen.

In anaemia or in heart failure, the arterial blood may be normally saturated with oxygen when air is breathed but the delivery of oxygen to the tissues is reduced. In these conditions oxygen therapy may benefit seriously ill patients by increasing the amount of dissolved oxygen in the blood. In carbon monoxide poisoning (p. 958) high pressures of oxygen favour the dissociation of carboxyhaemoglobin; such pressures may be achieved in hyperbaric chambers in which oxygen is breathed at a pressure of two atmospheres, or by inhalation of as high a concentration of oxygen as possible at atmospheric pressure.

Adverse Effects. Pure oxygen is both irritant and toxic if it is inhaled for more than a few hours. Premature infants develop retrolental fibroplasia if exposed to excessive concentrations of oxygen. Normal subjects notice cough and bronchial irritation, and in patients ventilated with high concentrations of oxygen for several days pulmonary oedema and consolidation ('white lung') may occur. If such patients require oxygen it is important to give, whenever possible, an inspired concentration which corrects hypoxaemia but does not exceed 60 to 70 per cent.

Technique of Oxygen Administration. Hypoxaemia is such a common consequence of respiratory diseases that oxygen may well be the most frequently prescribed 'drug' used in their treatment. It is important that prescriptions for oxygen should be in writing, and that flow rates or concentrations should be clearly specified. Administration of oxygen should be continuous; there is now no place for deliberate intermittent oxygen therapy, though continuous therapy may prove hard to maintain in confused or restless patients. The risk of fire should never be forgotten when any concentration of oxygen above atmospheric is given, and special precautions are needed in hyperbaric chambers.

Oxygen masks are of two types:

1. Those which are designed to produce a high concentration of O_2 in the inspired air. Examples of this type of mask are the Polymask (British Oxygen Co. Ltd.) and the M.C. mask (Medical and Industrial Equipment Ltd.), both of which deliver about 60 per cent O_2 when the flow rate is 4-6 *l* per min.

2. Those which are designed to produce slight O_2 enrichment of the inspired air and do not permit the rebreathing of expired CO_2. Examples of this type of mask are the Edinburgh mask (British Oxygen Co. Ltd.) and the Ventimask (Vickers Limited Medical Group). With the Edinburgh mask adjustments of the O_2 flow rate can provide inspired O_2 concentrations at any level between

23 and 35 per cent. The Ventimask is available in three models, which deliver 24, 28 and 35 per cent O_2 respectively.

Nasal Catheters. Double nasal cannulae fit comfortably into the nostrils. Their main advantages are that they do not permit rebreathing of CO_2 and do not interfere with eating, drinking and the wearing of spectacles. The inspired O_2 concentration they provide is somewhat unpredictable, but an O_2 flow rate of 2 *l*/min. will usually raise it to about 30 per cent.

Oxygen Tent. This is cumbersome, hampers nursing and physiotherapy and provides an extremely variable O_2 concentration because of leaks and repeated access by attendants. It has a place in the treatment of children and of adults who will not tolerate a mask provided they are not mentally confused because of hypercapnia.

Humidification. When Polymasks, M.C. masks or nasal cannulae are used, the oxygen must be humidified, either by passing it through a canister of warmed water or through a nebuliser. This is not necessary with Edinburgh masks or Ventimasks, as these masks entrain a high proportion of atmospheric air.

Treatment of Ventilatory Failure

1. **Acute Ventilatory Failure.** A clear airway is essential. In conscious patients this can often be secured and maintained by determined efforts to encourage expectoration, every 15 minutes or so at first, under the strict supervision of a doctor, nurse or physiotherapist. If this policy fails, and particularly if the patient has become confused or unconscious, a cuffed endotracheal tube should be inserted through the mouth or nose under general anaesthesia, and connected to a hand resuscitator (Ambu International, Copenhagen) or mechanical ventilator. At frequent intervals the trachea and bronchi should be cleared of secretions by aspiration through a soft catheter. Most patients are intolerant of artificial ventilation in the early stages, and require heavy sedation with opiates. The endotracheal tube can be left in place for up to 48 hours while treatment is continued. Some patients recover adequate spontaneous ventilation before the tube is due to be removed, but others require tracheostomy to allow tracheobronchial aspiration and mechanical ventilation to be continued for a longer period. Tracheostomy should usually be avoided in patients who have had severe respiratory disability for several months before the onset of ventilatory failure. Bronchoscopic aspiration may be of value as an initial measure to clear the airways of secretion, and if the patient can thereafter cough effectively tracheal intubation may not be required.

During manual or mechanical ventilation through an endotracheal tube the depressant effect of a high Pa_{O_2} on respiration can be ignored, and there is no objection to ventilating the patient with a high concentration (60 per cent or more) of O_2. When artificial ventilation is stopped, however, or in cases where it has not been employed, increasing hypercapnia is a potential hazard of O_2 administration, and the concentration of O_2 in the inspired air should initially be kept below 30 per cent by using a Ventimask, an Edinburgh mask or a double nasal cannula (p. 331). It is indeed seldom necessary or desirable to increase the inspired O_2 concentration above this level. When O_2, even in a concentration of 30 per cent or less, is being administered to patients with acute ventilatory failure, the P_{aCO_2} or P_{vCO_2} (p. 329) should be estimated at regular intervals. Patients who are critically ill require a more elaborate monitoring procedure, which should include frequent measurements of P_{aO_2}, P_{aCO_2}, and pH. An indwelling cannula in the brachial or radial artery can conveniently and safely be used for obtaining blood samples. If a steady increase in P_{aCO_2} is accompanied by clinical deterioration and/or by a fall in pH to below 7·25 units, artificial ventilation, either short-term via an endotracheal tube or long-term via a tracheostomy tube, should be started without delay. The disturbances in P_{aO_2}, P_{aCO_2} and pH can usually be corrected within 24 hours, but it may be several days before the patient is capable of maintaining a sufficiently high level of alveolar ventilation to allow him to dispense with mechanical assistance.

In all cases respiratory infection should be treated (p. 329). Water and electrolyte balance should be maintained, by intravenous infusion if necessary, as dehydration increases the viscosity of bronchial mucus and makes it difficult to aspirate.

Analeptic drugs have only a minor place in treatment. Nikethamide (2-4 ml of a 25 per cent solution one- to two-hourly) or doxapram (infusions of up to 3 mg/min.) given intravenously for 24 hours, may successfully tide the patient over a period of underventilation and obviate the need for tracheostomy, particularly if bronchial secretions are not present in large amounts. Although analeptic drugs seldom produce sustained stimulation of respiration, they may improve the level of consciousness and thus restore effective expectoration. Should sedation be necessary, diazepam is probably the drug least liable to depress respiration.

2. **Chronic Ventilatory Failure.** Many patients with progressive respiratory disease eventually enter a state in which P_{aO_2} and P_{aCO_2} never return to normal. In such patients, attempts to increase ventilation by orally administered drugs (such as the carbonic anhydrase inhibitor, dichlorphenamide) are sometimes advocated. However, there is no clear evidence that such treatment is beneficial and there is a possibility of doing harm. At present, therefore, treatment should be directed to the prevention of acute respiratory infections, the relief of airway obstruction and the management of coincident cardiac failure. In chronic ventilatory failure a worthwhile increase in exercise tolerance has been shown to result from the use of light, portable oxygen equipment. The provision of such equipment for all patients who could derive benefit from it presents a formidable problem. However, patients confined to their homes may be helped by the intermittent use of low concentrations of oxygen obtained from a static supply; it must be admitted that such benefit may often be psychological rather than physical. The potential benefits of continuous low-concentration oxygen therapy in the home are still under investigation.

Symptomatic Treatment in Respiratory Disease

Cough, when productive of sputum, should be encouraged and not suppressed. Those who are physically weak should be exhorted at regular intervals to clear their bronchi of secretion. Those with bronchiectasis or lung abscess should practise postural drainage, and those with tenacious sputum should be given hot drinks and inhalations of either steam or nebulised water to help them to bring it up more easily.

Unproductive, distressing cough should be suppressed. Demulcent lozenges are occasionally effective, but many patients require antitussive drugs, especially if sleep is disturbed by coughing. The two most effective preparations, suitable for general use in bronchitis, pneumonia, bronchial carcinoma and pulmonary tuberculosis, are pholcodine linctus (B.P.C.), and methadone linctus (B.P.C.), each given in a dose of 5-10 ml.

Airway obstruction in bronchitis and asthma is treated by bronchodilator drugs (p. 378) and in certain carefully selected cases by corticosteroids (p. 379).

Chest Pain. Pleural pain can usually be relieved by the application of a rubber hot-water bottle or by an electric heating pad to the chest wall, supplemented by an analgesic and, if necessary, by an antitussive drug. Mild analgesics, such as acetylsalicylic acid, or codeine compound tablets (B.P.C.), are adequate in most cases but a few patients may require pethidine, 50-100 mg by mouth or intramuscular injection, or even morphine, 10-15 mg subcutaneously. Opiates must, however, be avoided in patients with poor respiratory function and in those who have difficulty in coughing up sputum.

The pain of acute tracheitis usually responds to the application of heat to the front of the chest, combined with inhalations of steam medicated with benzoin (p. 340). Pain due to invasion of the chest wall by a malignant tumour, if not relieved by radiotherapy, usually demands a powerful analgesic such as pethidine or morphine, given by injection. In advanced cases these drugs may become ineffective and neurosurgical measures may be required for the relief of intractable pain.

INFECTIONS OF THE RESPIRATORY TRACT

Infections of the respiratory tract may be caused by large and small bacteria, by viruses and by fungi. 'Small' bacteria include coxiella causing Q-fever, mycoplasma causing pneumonia, and chlamydia causing psittacosis and ornithosis. The patterns of illness produced by small bacteria and viruses are summarised in Table 5, p. 337. Pulmonary tuberculosis and diseases caused by fungi are described in separate sections.

The number of viruses known to cause respiratory infection is continually increasing. They are universally distributed, of high infectivity and thus of great economic importance. The early diagnosis of virus infection is difficult because the excretion of some viruses is of short duration and the organisms die rapidly unless laboratory examination is undertaken quickly. Nasal and pharyngeal washings give a higher yield than throat swabs. Enteroviruses may be isolated from faeces over a longer period. Virus isolations are made on tissue cultures in various media including eggs and monkey kidney. More frequently a retrospective diagnosis is made from serological studies by neutralisation or complement-fixation tests. Serum specimens should be taken at the beginning of the illness and 10 to 14 days later. A four-fold rise in titre suggests a recent infection. Fluorescent antibody techniques and electron microscopy may provide more rapid diagnosis in the future.

Acute Coryza (Common Cold)

Aetiology. The early features are produced by primary infection of the nose and nasopharynx by a number of viruses (Table 5, p. 337), especially the rhinoviruses. Subsequent bacterial infection by *Strept. pneumoniae*, *H. influenzae* or staphylococci is usual. Infection is favoured by congregation in public places and bad housing, and resistance may be lowered by debility and sudden changes in environmental temperature and humidity. Immunity is short-lived and is specific for each virus strain.

Clinical Features. The onset is usually sudden with a tickling sensation in the nose accompanied by sneezing. The throat often feels dry and sore, the head feels 'stuffed', the eyes smart and there is a profuse watery nasal discharge. These symptoms last for one to two days, after which, with secondary infection, the secretion becomes thick and purulent, and impedes nasal breathing. There may be slight fever at the beginning.

Complications. It is hard to say whether variations in course represent complications of a standard illness or the primary effects of different viruses; probably both factors are involved, as well as resistance of the host.

1. *Sinusitis.* There is usually more systemic upset than in uncomplicated coryza. Headache is often present and may be severe, and there may be pain or discomfort over the face. Localised tenderness on palpation over the maxillary and frontal sinuses may be elicited.

For anatomical reasons already discussed (p. 312) sinus infection is liable to become chronic, particularly in the maxillary sinuses. The chief symptom of chronic sinusitis is persistent purulent discharge from the front and back of the nose, often accompanied by nasal obstruction and recurrent headaches. Local tenderness is not usually as marked as in the acute stage.

2. *Eustachian catarrh*, causing deafness, and *otitis media*, causing fever and aural pain.
3. *Lower respiratory infection.* Tracheitis, bronchitis, bronchiolitis and lobular pneumonia.

Diagnosis. If conjunctivitis is present in a child, measles must be considered. Frequent attacks of sneezing and watery rhinorrhoea, without systemic upset, suggest nasal allergy (p. 374) rather than virus infection.

Prevention. Much can be done to prevent the spread of coryza to others by voluntary isolation of patients for two to three days during the early, highly infectious stage. In persons who are liable to frequent colds the nose and throat should be examined for enlarged adenoids, polypi, infected sinuses and deflected septum, and any such abnormality corrected. The value of mixed catarrhal vaccines in the prevention of coryza has not been proved and their use is not recommended.

Treatment. No curative treatment for the common cold is known. The congestion and excessive secretion of the nasal mucous membrane may be reduced by the periodic use of 1 per cent ephedrine in normal saline either sprayed or dropped into the nose. Steam medicated with benzoin inhalation (B.P.C.) or menthol and benzoin inhalation (B.P.C.), 1 teaspoonful to 1 pint of boiling water, is beneficial, especially if the nasal sinuses are involved or there is obstruction of the Eustachian tubes. Antibiotic therapy is required only for the treatment of complications or as prophylaxis in those with cardiac or respiratory disease.

Pharyngo-conjunctival Fever

Aetiology. The pharyngeal syndrome, which is sometimes accompanied by conjunctivitis particularly amongst schoolchildren in spring and summer and in holiday camps, may be caused by several viruses (Table 5, p. 337) especially adenoviruses. *Herpangina* may occur in infections with Coxsackie A viruses.

Clinical Features. Conjunctivitis may be the first symptom, but sore throat is the dominant feature and may be slight or severe. The pharynx, tonsils and adenoids become inflamed and yellow exudate may be present. Cervical lymph nodes are enlarged and tender. The degree of constitutional symptoms—shivering, malaise, anorexia, headache and fever—is variable. In herpangina, typical vesicles, which may become punched-out ulcers, are present on the fauces.

Diagnosis. Acute streptococcal sore throat may be clinically indistinguishable, but *Strept. pyogenes* will be isolated from such cases. Infectious mononucleosis (p. 745) may also be difficult to differentiate from the pharyngeal syndrome in the early stages.

Treatment. Antibiotics are unnecessary. Gargles are often prescribed but are ineffective. Lozenges containing local anaesthetic, e.g. benzocaine compound lozenges (B.P.C.) are helpful when the throat is painful. A mild analgesic such as codeine compound tablets (B.P.C.) relieves systemic symptoms.

Acute Laryngo-tracheo-bronchitis

Aetiology. This illness, which is particularly serious in very young children because of the small calibre of their airways, may be caused by several viruses (Table 5, p. 337). Superinfection with bacteria, especially *Strept. pyogenes* and staphylococci may occur. The mucosa is intensely inflamed, the secretions are extremely tenacious and fibrinous casts of the bronchi may form.

Clinical Features. The initial symptoms may be those of the common cold (p. 335). These are followed by severe and sometimes violent cough which may be paroxysmal accompanied by dyspnoea and stridor ('croup'), contraction of accessory muscles and indrawing of intercostal spaces. The child may be

TABLE 5

Respiratory Disorders caused by Viruses, Chlamydia, Mycoplasma and Coxiella

Aetiological Agent	Clinical Syndrome (Excluding Pneumonia)	Pneumonia
Adenoviruses	Acute coryza Pharyngo-conjunctival fever Acute laryngitis	Occasional epidemics: cold agglutinins present
Coxsackie virus	Pharyngo-conjunctival fever Herpangina	
Echoviruses	Acute coryza Pharyngo-conjunctival fever	
Influenza virus A, B, (C)	Epidemic influenza Acute laryngo-tracheo-bronchitis (croup)	Primary rare: usually secondary infection with bacteria
Parainfluenza virus	Acute coryza Acute laryngo-tracheo-bronchitis (croup)	Primary rare: usually secondary infection with bacteria
Respiratory syncytial (RS) virus	Acute coryza Acute laryngo-tracheo-bronchitis (croup)	May cause severe and sometimes fatal bronchiolitis and pneumonia in infants
Rhinoviruses	Acute coryza	
Measles	Described on p. 84	Primary rare: usually secondary infection with bacteria
Chickenpox	Described on p. 88	Usually primary viral pneumonia: almost exclusively in adults
Chlamydia (psittacosis-ornithosis)		Primary pneumonia
Mycoplasma pneumoniae		Commonly in young adults: epidemics in institutions
Coxiella burneti (Q-fever)		Primary pneumonia

cyanosed, and asphyxia may occur if appropriate treatment is not given. The degree of systemic upset is variable.

Treatment. Warm humid air should be supplied by means of a steam kettle or tent. Clearing of secretions is of the utmost importance, and bronchoscopy and tracheostomy may be required as life-saving measures. As bacterial superinfection is often present, an antibiotic should be given. Attention to adequate hydration is also important and oxygen therapy may be necessary.

Influenza

Influenza is a specific acute illness caused by the influenza group of myxoviruses. It occurs in epidemics, and occasionally pandemics, often explosive in nature.

Aetiology. Three types of virus are described, A, B and C. Influenza A is responsible for the pandemics which occur from time to time. At least four strains have been identified and the so-called 'Asian' strain has been responsible for recent epidemics. Influenza B is usually associated with smaller and less virulent epidemics. The C virus is found only rarely. The immunity which follows is type-specific and of short duration. This causes problems in securing effective immunisation.

Clinical Features. The incubation period is one or two days. The illness starts suddenly with malaise, headache, pain in the back and limbs, anorexia and sometimes nausea and vomiting. Pyrexia to 39° C. (102° F.) remits for two or three days, with chills and shivering but seldom rigors. The face is flushed, conjunctivae suffused and fauces hyperaemic with prominent lymphoid follicles. The pulse is rapid. There is often leucopenia (2,000-4,000 per mm^3). There may be a harsh unproductive cough, without physical signs over the lungs. At this stage the case is indistinguishable clinically from a severe upper respiratory infection due to other respiratory viruses. The disease may spread rapidly throughout a household or institution.

Course and Complications. In many cases no further symptoms develop and recovery ensues within three to five days. The disease may, however, be complicated by tracheitis, bronchitis, bronchiolitis and lobular pneumonia. Secondary bacterial invasion by *Strept. pneumoniae*, *H. influenzae* and occasionally *Staph. pyogenes* causes these complications.

Toxic *cardiomyopathy* may cause sudden death, especially when there is pre-existing cardiac disease. *Encephalitis* and *post-influenzal demyelinating encephalopathy* are rare complications. *Post-influenzal asthenia* and *depression* are common, often marked, and may last for a week or two.

Diagnosis. During epidemics the diagnosis is usually easy. Most sporadic cases are identifiable only as respiratory virus infections unless the virus is isolated or serological tests for specific antibodies are positive.

Prevention. Immunity is type-specific and if the antigenic constitution of an epidemic can be detected early, a specific vaccine may give about 70 per cent protection. Annual winter vaccination is recommended for patients suffering from chronic pulmonary, cardiac or renal disease who are at special risk.

Treatment. Isolation at home is important to prevent spread of the disease. The patient should be kept in bed until fever has subsided. A mild analgesic such as codeine compound tablets (B.P.C.) 1-2, usually relieves the headache and backache. A linctus containing pholcodine or methadone (p. 334) may be used to suppress unproductive cough. The treatment of complications such as bronchitis (p. 340) and pneumonia (p. 352) is dealt with later.

Acute Catarrhal Laryngitis

Aetiology. Acute catarrhal laryngitis usually occurs either as a complication of coryza or as a manifestation of one of the infectious fevers, e.g. measles. It may also be caused by the inhalation of irritant gases.

Pathology. The laryngeal mucous membrane is swollen, congested and coated with mucus. Microscopically it is infiltrated with inflammatory cells. Rarely, in children, there may be a membranous exudate resembling diphtheria.

Clinical Features. The throat is dry and sore. The voice is at first hoarse and then reduced to a whisper. Speaking may be painful. There is an irritating, non-productive cough, but the general upset is usually mild. In children the small laryngeal opening may be obstructed by viscid secretion and spasm, giving rise to 'croup' (p. 336).

Treatment. The patient must be put to bed in a warm room and, to rest the larynx, he must not raise his voice above a whisper and must not smoke. Inhalations of medicated steam (p. 336) should be given three or four times a day, along with a linctus containing pholcodine or methadone (p. 334).

Prognosis. Acute laryngitis usually clears up in a few days, but if frequently repeated it may predispose to chronic laryngitis. Downward spread of the infection may cause tracheitis, bronchitis, or even pneumonia.

Acute Bronchitis

Aetiology. This condition is an acute inflammation of the trachea and bronchi caused by pyogenic organisms such as *Strept. pneumoniae*, *H. influenzae* and, less frequently, *Staph. pyogenes*. Infection by these organisms is a common sequel to coryza, influenza, measles and whooping-cough, and is particularly prone to develop in patients with chronic bronchitis.

Other factors predisposing to the development of infection include cold, damp, foggy and dusty atmospheres, smoking and chronic mouth breathing which allows unfiltered and unwarmed air to enter the bronchi.

Clinical Features. The first symptom is an irritating, unproductive cough accompanied by upper retrosternal discomfort or pain caused by tracheitis. When the bronchi become involved there is also a sensation of tightness in the chest, and dyspnoea with wheezing respiration may be present. Respiratory distress may be particularly severe when acute bronchitis complicates chronic bronchitis and emphysema. The sputum is at first scanty, mucoid, viscid and difficult to bring up, and occasionally may be streaked with blood. A day or two later it becomes mucopurulent and more copious. As the infection extends down the bronchial tree there is a general febrile disturbance, with a temperature of 38-39° C. (100-103° F.) and a neutrophil leucocytosis. In the vast majority of cases recovery takes place gradually over the next four to eight days without the patient ever becoming seriously ill. Occasionally the dyspnoea and general symptoms increase in severity, cyanosis appears, and if the infection reaches the smallest bronchi and bronchioles ('bronchiolitis') the condition becomes indistinguishable from lobular pneumonia.

Physical Signs in the Chest. Tracheitis without bronchitis produces no abnormal physical signs. In bronchitis there is no impairment of chest wall movement or percussion note. The breath sounds are vesicular, or vesicular with prolonged expiration, and are accompanied by *bilateral* rhonchi and, occasionally, coarse crepitations.

Course and Prognosis. The disease is usually mild and of short duration, the patient recovering within a few days if a suitable antibiotic is given. In severe cases it lasts longer, especially if bronchiolitis and lobular pneumonia develop.

Diagnosis. The diagnosis is usually easy, but it must not be forgotten that acute bronchitis may be an early and prominent manifestation of some underlying disease, such as measles or whooping-cough. When signs simulating those of acute bronchitis are confined to one part of the chest, pulmonary tuberculosis, bronchial carcinoma and bronchiectasis should be considered. Attacks of pulmonary oedema (p. 245) sometimes cause confusion in diagnosis.

Treatment. The patient should be confined to bed. If the attack is mild, phenoxymethylpenicillin, 250 mg four times daily, should be given by mouth. When the illness is more severe, tetracycline or ampicillin, 250-500 mg four times daily, should be substituted for penicillin. Co-trimoxazole, a combination of trimethoprim and sulphamethoxazole, is equally effective. In the early stages, when cough is painful and unproductive, the tough viscid secretion should be loosened by the inhalation three or four times a day of steam medicated with benzoin or menthol. A steam kettle or steam tent may be even more effective, particularly for children or elderly patients. The cough should be controlled at night by the use of a sedative linctus containing pholcodine or methadone (p. 334). If retrosternal discomfort is troublesome, heat may be helpful, applied to the chest by means of a hot bottle or an electric pad. If symptoms or signs of airway obstruction are present a bronchodilator drug (p. 378) may be of some value. Oxygen (p. 330) may be required.

The Pneumonias

Pneumonia is the term used to describe inflammation of the lung. There are many different kinds of pneumonia, some common, others rare. Aetiologically they can be divided into two broad groups:

1. **The Specific Pneumonias,** in which the disease is caused by a specific pathogenic organism.

2. **The Aspiration Pneumonias,** in which some abnormality of the respiratory system predisposes to the invasion of the lung by organisms of relatively low virulence. As the term implies, infection generally reaches the alveoli by aspiration from other parts of the respiratory tract. Failure to isolate pathogens is quite common. *H. influenzae*, some types of *Strept. pneumoniae* and certain of the bacteria forming the flora of the upper respiratory tract and mouth are organisms most frequently cultured from the sputum.

In certain types of specific and aspiration pneumonia, destruction of lung tissue by the inflammatory process, a high incidence of abscess formation and the subsequent development of pulmonary fibrosis and bronchiectasis are prominent features. The term '*suppurative pneumonia*' has been applied to this group of cases and this condition merits separate description (p. 349).

The Specific Pneumonias

This group may be further subdivided into pneumonias caused by (1) 'large' bacteria, and (2) viruses and 'small' bacteria.

Large bacteria known to produce specific types of pneumonia are *Strept. pneumoniae, Staph. pyogenes, Klebsiella pneumoniae, H. influenzae* and *Mycobacterium tuberculosis*.

Many viruses, including those described in Table 5 (p. 337), may produce a specific pneumonia, as may small bacteria such as *Coxiella burneti* (Q-fever), *Mycoplasma pneumoniae* and *Chlamydia* of the ornithosis (psittacosis) group.

Pneumonia due to the pneumococcus still constitutes the largest proportion of all specific pneumonias and will be described in detail. Shorter accounts will be given of the other types.

Pneumococcal Pneumonia

(*Syn.: Acute Lobar Pneumonia*)

Pneumococcal pneumonia is characterised by homogeneous consolidation of one or more lobes or segments.

Aetiology. The disease occurs at all ages but most frequently in early and middle adult life. The highest incidence is in winter. It is usually a sporadic disease, the mode of spread being by droplet infection.

Pathology. The pneumonic process usually affects only one lobe or segment but the infection may spread to other lobes or segments in the same or opposite lung. There is coincident inflammation of the overlying pleura. The affected lobes or segments undergo consolidation in which there is exudation of fibrin, red blood cells and later white blood cells into the alveoli. Resolution is achieved first by liquefaction of the exudate by macrophages and then by its absorption or expectoration. Resolution is usually complete: fibrosis and bronchiectasis seldom follow this type of pneumonia.

Clinical Features. The onset is sudden, with rigor, or with vomiting or a convulsion in children. The temperature rises in a few hours to 39-40° C. (102-104° F.). Malaise, loss of appetite, headache, and aching pains in the body and limbs accompany the pyrexia. Localised pain of pleural type (p. 321) develops at an early stage in the illness. It is generally referred to the chest wall but may on occasion be referred to the shoulder or to the abdominal wall, when it may be difficult to determine whether the primary lesion is in the chest or abdomen. There is a short, painful cough, dry at first but later productive of tenacious sputum which is often rust-coloured and occasionally frankly blood-stained. Respiration is rapid (30 to 40 per minute in adults, 50 to 60 in children), shallow and painful, and there may be dilatation of the alae nasi with each inspiration. The pulse is rapid, and in severe cases the blood pressure tends to fall. The skin is hot and dry, the face is flushed, and cyanosis may occur early. Herpes labialis is often present. A marked neutrophil leucocytosis, 15,000-30,000 per mm^3, is characteristic. The causative pneumococcus can usually be isolated from the sputum, and a positive blood culture may be obtained in severe cases.

Course. Most cases respond promptly to the administration of an antibiotic. Within 24 to 48 hours of the start of treatment the temperature falls to 37° C. (98-99° F.), the pulse and respiration rates drop sharply, cyanosis disappears and the systemic disturbance is dramatically relieved. The cough, sputum and pleural pain take rather longer to subside but seldom remain for more than a few days, and within a week the patient is well again. Delayed recovery suggests either that some complication has developed (e.g. empyema) or that the diagnosis of pneumococcal pneumonia is incorrect.

Occasionally in old or debilitated persons the response to treatment is unsatisfactory. The symptoms rapidly become worse, there is increasing weakness, dyspnoea, cyanosis and delirium, and death takes place within a few days from hypoxia or peripheral circulatory failure. A fatal outcome is more liable to occur if there has been a delay in starting specific treatment.

Physical Signs in the Chest. For the first 24 to 48 hours of the illness there is diminution of respiratory movement, slight impairment of the percussion note, and often a pleural rub on the affected side. The breath sounds are diminished vesicular, and fine crepitations may be heard at the end of inspiration. At a variable time after the onset, generally within two days, signs of consolidation appear (p. 326), the breath sounds being of the high-pitched bronchial type. When resolution begins, these breath sounds are replaced by low-pitched bronchial breath sounds, which later revert gradually to normal vesicular. Numerous coarse crepitations are heard, indicating liquefaction of the exudate.

The physical signs may be modified in the following circumstances: (1) if the pneumonic process does not extend to the periphery of the lung, there may be no abnormal physical signs throughout the illness; (2) if a bronchus is blocked by secretions, signs suggestive of collapse may be found (p. 326), but mediastinal displacement is usually absent, as a consolidated lobe cannot shrink to the same degree as a healthy lobe; (3) if a sterile or purulent effusion develops, the physical signs of fluid in the pleural space are usually found (p. 326), but often bronchial breath sounds persist and the presence of an effusion may be suspected only from the stony dullness of the percussion note.

Radiological Examination. This shows a homogeneous opacity localised to the affected lobe or segment, appearing within 12 to 18 hours of the onset of the illness. Radiological examination is particularly helpful when the diagnosis is in doubt or if a complication such as empyema is suspected.

Complications. 1. PULMONARY.

(*a*) *Spread to other lobes.* This may occur but is uncommon.

(*b*) *Delayed resolution.* Resolution is less rapid in older patients, in those with chronic bronchitis and emphysema, and in cases where the consolidation has originally been very extensive. In 85 per cent of all cases the abnormal physical signs disappear within two weeks and the radiological opacity within four weeks. Although resolution is occasionally delayed for longer periods in uncomplicated pneumococcal pneumonia, such delay is often due to the presence of some underlying lesion such as bronchiectasis or bronchial carcinoma. This possibility must always be kept in mind when a pneumonia is slow to resolve.

2. PLEURAL. Spread of the infection to the pleura may occur with the development of a sterile *pleural effusion* (p. 414) or *empyema* (p. 418).

3. CARDIOVASCULAR.

(*a*) *Peripheral circulatory failure* (p. 251).

(*b*) Acute pneumococcal *pericarditis* and *endocarditis* (rare).

4. NEUROLOGICAL.

(*a*) *Meningism.* This is not uncommon in children, and lumbar puncture may be required to distinguish it from meningitis (p. 855).

(*b*) Pneumococcal *meningitis* (rare).

Diagnosis. The characteristic features of pneumococcal pneumonia are the initial rigor, herpes labialis, the physical signs of consolidation, a high neutrophil leucocyte count, pneumococci in the sputum, a lobar or segmental radiological opacity and a rapid and complete response to treatment with an antibiotic.

The following conditions may be difficult to distinguish from pneumococcal pneumonia:

1. *Other types of acute specific and aspiration pneumonia* (pp. 344-346).
2. *Pulmonary infarction* (p. 282), in which pyrexia is less marked and is

uninfluenced by antibiotics, frank haemoptysis is common, cough is inconspicuous and the site of origin of the embolus can often be identified.

3. *Tuberculous pleurisy with effusion*, in which the correct diagnosis can usually be suspected from the insidious onset, the virtual absence of cough and sputum, the physical signs of pleural effusion, the absence of leucocytosis, the failure of the pyrexia to respond to antibiotics, the radiological findings and the aspiration of serous fluid, in which lymphocytes predominate, from the pleural space.

4. *Pulmonary tuberculosis*, acute cases of which may simulate pneumonia. The patient is, however, seldom as acutely ill as in pneumococcal pneumonia; it is uncommon for the respiratory rate to be markedly increased and the white blood count is seldom above 12,000 per mm^3. The diagnosis can usually be made by radiological examination, and the isolation of tubercle bacilli from the sputum puts it beyond doubt.

5. *Pulmonary collapse*, in which the diagnostic difficulty is usually caused by the presence of infection (aspiration pneumonia) in the collapsed lung tissue. If the breath sounds are reduced or absent and there are signs of mediastinal displacement to the same side, collapse is probably present, but often the symptoms and signs are indistinguishable from those of pneumococcal pneumonia and the correct diagnosis can be made only by radiological examination.

6. *Acute bronchitis*, in which the onset is less abrupt and the systemic disturbance less severe than in pneumococcal pneumonia. Pleuritic pain is not present and the physical signs and radiological appearances of pneumonic consolidation are not found.

7. *Inflammatory conditions below the diaphragm*, such as cholecystitis, perforated duodenal ulcer, acute appendicitis, subphrenic abscess, generalised peritonitis and hepatic amoebiasis, may occasionally be mistaken for pneumococcal pneumonia. A carefully taken history is one of the most valuable means of determining the site and nature of the primary disease. A high temperature and a very rapid respiratory rate favour a diagnosis of pneumonia, whereas tenderness of the abdominal wall suggests that the primary lesion is below the diaphragm. Sometimes radiological examination of the chest is necessary before the presence of pneumonia can be confirmed or excluded.

Prognosis. The prognosis depends on the virulence of the infecting pneumococcus, the age of the patient (the mortality rises above the age of 60), the general state of health (the mortality is increased when pneumonia complicates other serious disease or develops in a chronic alcoholic), and the stage of the illness at which specific treatment is instituted. The prognosis is less favourable in the absence of a brisk temperature response or when there is a poor leucocytosis, marked cyanosis, delirium or peripheral circulatory failure, or extension of the disease to other lobes.

Other Types of Specific Pneumonia

1. **Staphylococcal Pneumonia.** Pneumonia due to *Staph. pyogenes* may occur either as a primary respiratory infection or as a blood-borne infection from a staphylococcal lesion elsewhere in the body, e.g. osteomyelitis. The second

condition is essentially one of pyaemic abscess formation in the lungs. Unless an empyema is produced by rupture of one of these abscesses into the pleura, the pulmonary lesions may pass unnoticed, overshadowed by the severe general illness.

Primary staphylococcal pneumonia, although it occurs much less frequently than pneumococcal pneumonia, is a relatively common illness, especially as a complication of influenza. It may present as a lobar or segmental pneumonia, which may be difficult to distinguish clinically from a severe pneumococcal infection, or as a suppurative pneumonia (p. 349) with multiple lung abscesses which may persist as thin-walled cysts after the acute infection has subsided. Culture of the sputum yields a growth of coagulase-positive staphylococci which are frequently resistant to penicillin, streptomycin, tetracycline and chloramphenicol. At the present time few strains of staphylococci causing pneumonia are resistant to erythromycin, cloxacillin, cephaloridine or sodium fusidate, but this relatively favourable situation may alter if these drugs are prescribed on a larger scale in future.

2. **Klebsiella Pneumonia (Friedländer's Pneumonia).** Pneumonia due to *Klebsiella pneumoniae* is a rare disease. There is usually massive consolidation and excavation of one or more lobes, the upper lobes being most often involved, with profound systemic disturbance, the expectoration of large amounts of purulent, sometimes chocolate-coloured, sputum and a high mortality. The diagnosis is made by the radiological appearances and the isolation of the causative organism from the sputum. Streptomycin plus chloramphenicol is the first choice in antibiotic therapy, but treatment should be modified according to the results of sensitivity tests.

3. **Tuberculous Pneumonia** (p. 363).

4. **Pneumonia Caused by Viruses and Small Bacteria.** A distinctive form of pneumonia may be produced by certain viruses, and by small bacteria (p. 346), which exhibit a similar pathogenicity to lung tissue (Table 5, p. 337).

The pneumonia caused by each of these organisms gives rise to a similar clinical picture, which differs from that of the bacterial pneumonias in that fever and toxaemia usually precede the respiratory symptoms by several days. Severe headache, malaise and anorexia are characteristic features in the early stages. The physical signs in the chest, if there are any, appear later and are seldom gross. The existence of a pulmonary lesion may not be recognised unless a radiograph is taken. The spleen may be palpable in the first week. The white blood count is generally normal and the pyrexia does not respond to penicillin. If facilities for virological investigation are available the diagnosis can often be confirmed by isolation of the virus or by serological tests.

The disease is usually self-limiting. The pyrexia subsides by lysis after 5 to 10 days, and complete recovery and radiographic resolution follow, the latter sometimes being slow. Very rarely, death takes place from widespread extension of the pneumonia or from virus encephalitis.

The *influenza*, *parainfluenza* and *measles* viruses rarely produce a specific pneumonia. The pneumonia caused by *chickenpox* virus (p. 88), however, is usually characteristic. The radiograph shows numerous miliary nodular shadows which may eventually calcify. It occurs almost exclusively in adults. The *adenoviruses* cause occasional mild epidemics of specific pneumonia, cold agglutinins being present in many cases.

Respiratory syncytial virus is the most important respiratory pathogen of early childhood, especially in the first two months of life. This is because it causes bronchiolitis and pneumonia and carries an important risk of mortality in this age-group. The infant is fevered, and cough, wheezy respiration and occasionally an erythematous rash are prominent features. The virus is not susceptible to any known antibiotic, and immunisation is ineffective.

Psittacosis (parrot-fever) and *ornithosis* are caused by organisms of the *Chlamydia* family. They used to be considered as viruses but they have been shown to have the structural and biochemical properties of bacteria and rickettsiae. The diseases are primarily infections of birds and are transmitted to humans by inhalation of dust containing faeces from infected birds. The pneumonia caused by these organisms, which are susceptible to tetracyclines, is occasionally extensive and associated with severe toxaemia.

Mycoplasma pneumoniae is not a virus but a pleomorphic bacterium capable of passing through a filter. It is susceptible to tetracyclines though a few strains are sensitive only to erythromycin. Cold agglutinins can be demonstrated in a high proportion of cases. Antibodies can be detected and haemagglutination and complement-fixation tests are available for diagnosis. Outbreaks of pneumonia caused by this organism are common in barracks and institutions. Most cases occur in children and young adults.

Coxiella (*Rickettsia*) *burneti* is the organism responsible for *Q-fever*. The usual sources of infection are cattle and sheep. Endocarditis may be present as well as pneumonia in this disease. The diagnosis is made by examining specimens of serum at an interval of two weeks.

The Aspiration Pneumonias

Aetiology. This group, sometimes described as the non-specific pneumonias, comprises a large number of different conditions, their common features being the absence of any specific pathogenic organism in the sputum and the existence of some abnormality of the respiratory system which predisposes to the invasion of the lungs by relatively avirulent organisms derived from the upper respiratory tract or from the mouth, e.g. streptococci, certain types of pneumococci, *H. influenzae*, Vincent's spirochaetes and fusiform bacilli.

Infection may reach the lungs in various ways. Pus may be aspirated from an infected nasal sinus, or septic matter may be inhaled during tonsillectomy or dental extraction under general anaesthesia. Vomitus or the contents of a dilated oesophagus may enter the larynx during general anaesthesia, coma or even sleep. Infected secretion in the bronchi and pus from bronchiectatic cavities or from a lung abscess may also be carried into the alveoli by the air stream or by gravity.

Ineffective coughing caused by post-operative or post-traumatic thoracic or abdominal pain, by debility or immobility, or by laryngeal paralysis may also predispose to the development of aspiration pneumonia.

Bronchial obstruction, partial or complete, as for example by a carcinoma, is another potential cause of aspiration pneumonia, as it allows infection derived from the upper air passages to become established in the inadequately ventilated portion of lung beyond the obstruction.

There are *four* types of aspiration pneumonia with fairly well-defined clinical and pathological features: (1) acute lobular pneumonia, (2) benign aspiration pneumonia, (3) hypostatic pneumonia, and (4) post-operative pneumonia.

1. ACUTE LOBULAR PNEUMONIA

(*Syn.: Acute Bronchopneumonia*)

This type of pneumonia is invariably preceded by bronchial infection, which accounts for the widespread, lobular distribution of the lesions. It occurs most frequently in children and in elderly people. In children it is often a complication of measles or whooping-cough, in adults of acute bronchitis or influenza. It is particularly common in patients with chronic bronchitis and emphysema.

Pathology. There is acute inflammation of the bronchi, especially the terminal bronchioles, which are filled with pus. Collapse and consolidation of the associated groups of alveoli follow. The lesions are distributed bilaterally in small patches which tend to become larger by confluence and are often more extensive in the lower lobes. The alveolar exudate consists of neutrophil leucocytes with a small amount of fibrin. There is interstitial oedema and cellular proliferation in the alveolar walls, and compensatory emphysema around the collapsed alveoli. Resolution of lobular pneumonia may be incomplete, and in such cases pulmonary fibrosis and bronchiectasis are common sequelae.

Clinical Features. The patient first exhibits for two or three days the clinical features of acute bronchitis and then, as lobular pneumonia develops, the temperature rises to a higher level, the pulse and respiratory rates increase, and dyspnoea and cyanosis appear. There is generally a severe cough with purulent sputum. Pleural pain is relatively uncommon and herpes labialis is seldom present, in contrast to pneumococcal pneumonia. Blood examination shows a neutrophil leucocytosis.

Physical Signs in the Chest. During the early stages the signs are those of acute bronchitis (p. 339) but crepitations later become more numerous. In many cases no signs of consolidation can be detected, but these may develop when lobular lesions coalesce.

Radiological Examination. Mottled opacities are present in both lung fields, chiefly in the lower zones.

Course and Complications. The disease tends to run a more protracted course than pneumococcal pneumonia (7 to 10 days). Incomplete resolution may lead to bronchiectasis, but the number of patients developing this complication has fallen dramatically since antibiotics became available.

Diagnosis. Lobular pneumonia differs from pneumococcal pneumonia in its insidious onset and in the history of antecedent bronchitis. The physical signs and radiographic changes are typically bilateral and diffuse.

Prognosis. The mortality is higher at the extremes of life, especially if the disease is associated with malnutrition or if it supervenes on chronic bronchitis and emphysema, chronic nephritis or heart disease.

Prophylaxis. The incidence of lobular pneumonia can be reduced by careful attention to apparently benign upper respiratory infections such as coryza and acute bronchitis, especially when they occur at the extremes of life and in patients with chronic bronchitis. Measures to prevent whooping-cough and measles, and adequate treatment of those diseases, are also important in prophylaxis (pp. 65, 85).

2. Benign Aspiration Pneumonia

This type of pneumonia is due to the aspiration of infective secretion into the lungs during the course of an upper respiratory infection such as coryza or sinusitis. It is thus often associated with segmental pulmonary collapse. The organisms causing the pneumonia, being derived from the upper respiratory tract, are generally of low virulence and the degree of systemic disturbance is usually slight. In fact, the symptoms are often no more severe than would be expected with an uncomplicated upper respiratory infection and the existence of a pneumonia may be discovered only by radiological examination. As a rule, however, the condition manifests itself by cough, purulent sputum, low-grade pyrexia and sometimes pleuritic pain, in association with a frank upper respiratory infection. Localised coarse crepitations are often the only abnormal physical signs. Leucocytosis is absent or slight. The radiological lesions are usually *unilateral*, the characteristic appearance being a mottled opacity involving a single lobe or segment, which in some cases may be collapsed.

The condition is liable to be confused with virus pneumonia because of the paucity of pulmonary symptoms and signs and the normal white blood count, but the co-existent upper respiratory infection and the minimal systemic upset are useful distinguishing features. Pulmonary tuberculosis may be erroneously diagnosed on the basis of a single radiograph. Re-examination 10 to 14 days later, following treatment with an antibiotic, will resolve the diagnosis as recovery is generally rapid in aspiration pneumonia. As suppuration is not a feature of this type of pneumonia, permanent lung damage and bronchiectasis rarely occur.

3. Hypostatic Pneumonia

This type of aspiration pneumonia occurs in elderly or debilitated people and is a common cause of death. These patients, being physically weak and immobilised in bed, have difficulty in expectorating bronchial mucus and the alveolar transudate which tends to form as a result of hypostatic pulmonary congestion. These secretions gravitate to the bases of the lungs where infection, usually with upper respiratory commensal organisms, frequently supervenes.

The lobular pneumonia which results is a relatively mild process but is sufficient to cause death in patients enfeebled by old age, heart failure or toxaemia.

The onset of symptoms in hypostatic pneumonia is insidious, often almost imperceptible at first. A slight cough accompanied by an increase in pulse and respiration rates is usually the earliest manifestation. Pyrexia and leucocytosis may occur but are seldom marked. Physical signs in the chest are usually bilateral and confined to the lower lobes. Frank signs of consolidation may be present, but numerous coarse crepitations at both lung bases without signs of consolidation are a more common finding. Once the condition is established it pursues a rapidly fatal course, usually with little apparent discomfort to the patient.

Preventive measures are all-important. Elderly people should not be confined to bed unless this is absolutely necessary. Patients who have to be kept in bed should have their position changed frequently and be given deep-breathing exercises.

4. Post-operative Pneumonia

Primarily this condition is not pneumonia but pulmonary collapse due to obstruction of a large bronchus by viscid secretion which cannot be expectorated owing to post-operative pain. Infection may occur secondarily with the production of an aspiration pneumonia. The condition is more fully described on page 400.

Suppurative Pneumonia

(*Including Pulmonary Abscess*)

Suppurative pneumonia is the term used to describe a form of pneumonic consolidation in which there is destruction of lung parenchyma by the inflammatory process. Although abscess formation is a characteristic histological feature of suppurative pneumonia, it is usual to restrict the term 'pulmonary abscess' to lesions in which there is a fairly large localised collection of pus, or a cavity lined by chronic inflammatory tissue, from which pus has been evacuated.

Aetiology. Suppurative pneumonia and pulmonary abscess may be produced by infection of previously healthy lung tissue with *Staph. pyogenes* or *Klebsiella pneumoniae*. These are, in effect, specific bacterial pneumonias associated with pulmonary suppuration.

More frequently, suppurative pneumonia and pulmonary abscess are forms of aspiration pneumonia. They may develop after the inhalation of septic material during operations on the nose, mouth or throat under general anaesthesia, or of vomitus during anaesthesia or coma. In such circumstances gross oral sepsis is an important predisposing factor. Bacterial infection of a pulmonary infarct or of a collapsed lobe may also produce a suppurative pneumonia or a pulmonary abscess. The organisms isolated from the sputum may include *Strept. pneumoniae*, *Staph. pyogenes*, *Strept. pyogenes*, *H. influenzae* and, in a few cases, anaerobic streptococci and other anaerobes such as Vincent's spirochaetes and fusiform bacilli. In some cases, however, no pathogens can be identified and the illness remains entirely unexplained.

Pathology. Descriptions have already been given of staphylococcal pneumonia (p. 344) and of klebsiella pneumonia (p. 345). When suppurative pneumonia follows the inhalation of infective material from the upper air passages, it is more often unilateral than bilateral, and is usually situated in the axillary part of either upper lobe or in the apex of a lower lobe, these being the most dependent areas when the patient is lying on his side or on his back respectively. In other cases the site depends on the nature and situation of the primary pathological lesion. For example, when the abscess is secondary to bronchial obstruction by a carcinoma its site is determined by the position of the tumour in the bronchial tree.

In suppurative pneumonia destruction of lung parenchyma leads to pulmonary fibrosis and bronchiectasis (p. 393). Usually the suppurative process is localised but occasionally it spreads by direct continuity until a whole lung is irreparably damaged. Abscesses, when present, may be single or multiple. Occasionally they may become very large as a result of inflation caused by a 'check valve' mechanism at the junction of the cavity and the draining bronchus.

Clinical Features. These depend to a large extent on the pathogenesis of the lesion. The onset of the illness may be either insidious or acute, but cough with purulent sputum, usually large in amount, sometimes foetid and occasionally blood-stained, is present from an early stage. There is high, remittent pyrexia with shivering and sweating, and a neutrophil leucocytosis in the region of 15,000-25,000 per mm^3. Pleural pain is common and clubbing of the fingers may develop as early as 10 to 14 days after the onset of the illness. Progressive deterioration in general health with marked loss of weight ensues if the patient remains untreated. The rupture of a large localised abscess into a bronchus can be assumed when a large quantity of pus is suddenly expectorated. Such an incident is often preceded by blood-staining of the sputum and followed by remission of the pyrexia.

Physical Signs in the Chest. These also depend on the nature of the primary pathological process. Signs of consolidation (p. 326) are the most frequent finding, but those of collapse are also common. Frank signs of cavitation are rarely found. Localised coarse crepitations may be the only abnormality. A pleural rub is often present.

Radiological Examination. There may be a homogeneous lobar or segmental opacity consistent with consolidation or collapse. Alternatively, if the lesions are of lobular distribution, multiple coarse, mottled opacities may be found. A large homogeneous opacity, which may later cavitate and show a fluid within it, is the characteristic finding when a frank pulmonary abscess is present.

Diagnosis. This cannot be considered complete unless the primary aetiological factor or factors are identified. Sputum should be sent for bacteriological examination, and if a pathogenic organism is isolated its sensitivity to the various antibiotics should be determined.

Suppurative pneumonia must be distinguished from:

1. Pulmonary tuberculosis, by examination of the sputum for tubercle bacilli.
2. Bronchial carcinoma, by bronchoscopy.

Pulmonary abscess must be distinguished from:

1. Pulmonary tuberculosis with cavitation, by examination of the sputum for tubercle bacilli.
2. A cavitated malignant growth, by the radiological appearances and, if necessary, by bronchoscopy.
3. Empyema, which gives the physical signs of fluid in the pleural space and from which pus can be obtained by paracentesis.

Course and Prognosis. Untreated, the disease carries a high mortality; those who survive are liable to recurrences of infection and some develop bronchiectasis. Empyema is a not uncommon early complication. Metastatic cerebral abscess may occur. Since the introduction of antibiotics the mortality has fallen sharply and many cases now escape with relatively little lung damage and bronchiectasis.

Prophylaxis. Every precaution should be taken during operations on the mouth, nose and throat to prevent the inhalation of blood, tonsillar fragments, etc. Oral sepsis should be eradicated, especially if a general anaesthetic is contemplated. Bronchial obstruction should be treated whenever possible. When the obstructing agent is tenacious secretion, this can readily be removed by postural coughing or bronchoscopic aspiration. When the obstruction is due to a bronchial carcinoma, resection of the lung or lobe containing the growth is the only effective treatment.

Mucoviscidosis (Cystic Fibrosis)

This is a hereditary disease characterised by generalised dysfunction of the exocrine glands, especially the pancreas, associated with an increase in viscosity of sputum and a high sodium chloride content of sweat. It is a chronic debilitating disease, mainly affecting children, and associated with a high mortality. The precise cause of the defect, which is transmitted as a recessive gene, is unknown.

Pathology. The excessive production of abnormally viscid sputum leads to bronchial obstruction and inflammation of the lungs. Varying degrees of bronchiectasis (p. 393) occur and there are patchy areas of collapse with fibrosis and emphysema. Pneumonia and lung abscess are common complications. Cor pulmonale (p. 284) may supervene. The pancreas shows characteristic obstructive changes in the ducts. The sweat, salivary and parotid glands produce an abnormal secretion but are histologically normal.

Clinical Features. The presenting feature is commonly the occurrence of repeated attacks of respiratory infection in early life. Consequent on defective pancreatic secretion the stools are bulky, foamy and foul-smelling as a result of malabsorption of fat. The child is often poorly nourished. As the disease progresses cough becomes severe and wheeze is often present. The clinical features of bronchiectasis (p. 394) develop and there is progressive dyspnoea and cyanosis. Cor pulmonale (p. 284) occurs in the terminal stages of the disease. The diagnosis is usually established by the finding of an increase in the concentrations of sodium and chloride in sweat to above 70 mEq/*l*.

Radiological Features. These are variable, depending on the stage of the disease. The features of pneumonia (p. 343), lobular pneumonia (p. 347), pulmonary collapse (p. 398) and emphysema (p. 391) may be present.

Course and Prognosis. Until the advent of antibiotics the prognosis was very poor, and most children died before puberty. However, with skilled medical treatment, an increasing number of patients are surviving into adult life.

Treatment. The management of this disease is best conducted from special centres. Both the child and the parents require long-term support. Physiotherapy to encourage drainage of pulmonary secretions and special measures to humidify sputum are important. Antibiotic therapy, adapted to the sensitivity of the organism, may need to be prolonged. Staphylococci are commonly found in sputum and gram-negative organisms such as *Proteus sp.*, *E. coli* and *Pseudomonas* may prove difficult to eradicate. The management of pancreatic insufficiency is discussed on page 485.

The Treatment of Pneumonia

1. **Chemotherapy.** The principles governing the specific treatment of bacterial infections of the respiratory tract have already been stated (p. 329). When a clinical diagnosis of pneumonia is made, provided the patient is not gravely ill, the initial treatment should consist of benzylpenicillin, 0·5-1 mega unit twice daily by intramuscular injection. Where the pneumonia has developed in a patient with chronic bronchitis, tetracycline or ampicillin, 250 mg four times daily, or co-trimoxazole, 2 tablets twice daily, should be substituted for penicillin in order to control the infection with *H. influenzae* frequently present in such cases. Patients who are gravely ill and in whom a staphylococcal infection is suspected should receive, in addition to penicillin, tetracycline or ampicillin, an antibiotic to which the organism is unlikely to be resistant, e.g. cloxacillin, 500 mg six-hourly by mouth or 250 mg six-hourly by intramuscular injection, or erythromycin, 500 mg six-hourly by mouth. Alternatively cephaloridine by intramuscular injection or cephalexin orally (p. 99) may be given in an initial dose of 4 g daily, which can be reduced to 2 g daily when a satisfactory clinical response has been obtained.

As soon as the results of bacteriological examination of the sputum are available and the drug sensitivity of the organism is known, usually 48 hours after treatment is started, the choice of antibiotic must be reviewed:

(*a*) If *Strept. pneumoniae*, *Strept. pyogenes* or an anaerobic streptococcus is isolated, or no pathogenic organisms are obtained on culture, and the patient appears to be making satisfactory clinical progress, parenteral therapy with benzylpenicillin may be stopped and phenoxymethylpenicillin, 250 mg four times daily, given by mouth. In patients with chronic bronchitis, treatment with tetracycline or ampicillin, 250 mg four times daily by mouth, should be maintained.

(*b*) If *Staph. pyogenes* is isolated, treatment must be modified in accordance with the results of sensitivity tests. In the unlikely event of the organism being sensitive to benzylpenicillin, no change in antibiotic need be made. If it is resistant to penicillin, treatment with streptomycin, tetracycline or chloramphenicol is seldom effective, even if *in vitro* sensitivity to these antibiotics is reported, and two of the following antibiotics will usually be required: cloxacillin, 500 mg four times daily, erythromycin, 250-500 mg four times daily, or sodium fusidate, 500 mg thrice daily (all by mouth).

(*c*) If *Klebs. pneumoniae* is isolated, sensitivity tests will indicate which drug is likely to prove most effective. Those to which this organism is most frequently sensitive are streptomycin, chloramphenicol, ampicillin, kanamycin and co-trimoxazole. The drug selected should be given initially in twice the standard dosage.

(*d*) If bacteriological examination is uninformative and a virus pneumonia is suspected, it is advisable to give an antibiotic to prevent or control secondary bacterial infection. In these circumstances tetracycline is the drug of choice as it has the advantage of possessing some degree of activity against organisms such as *Coxiella burneti*, *Mycoplasma pneumoniae* and *Chlamydia*. A dose of 500 mg four times daily is recommended.

It is important to take into account the clinical progress in addition to the bacteriological findings before changing from one antibiotic to another. If, for example, recovery is progressing satisfactorily, the isolation of an organism showing *in vitro* resistance to the antibiotic in use is not necessarily an indication for a change in treatment. If, however, the patient is not improving and is still febrile when such an organism is isolated, an appropriate change in antibiotic is imperative.

The impulse to substitute another antibiotic, *where there is no bacteriological indication for doing so*, should be resisted. The failure of patients to respond to treatment may be due to a complicating factor such as pleural infection, tuberculosis or bronchial obstruction by a tumour, and these conditions must be carefully excluded before the antibiotic is changed. In older patients particularly, radiographs should be repeated to ensure that tumour or tuberculosis has not been overlooked.

No hard and fast rule can be laid down for the *duration* of chemotherapy. In most cases of uncomplicated pneumococcal pneumonia a seven-day course of treatment is usually adequate but this may have to be extended if the response to treatment is slow. In staphylococcal and klebsiella pneumonia, and in other forms of suppurative pneumonia, chemotherapy should be continued for a minimum of two weeks and should not be stopped until the causative organism has been eliminated from the sputum.

2. **General Measures.** The usual regimen of treatment for an acute infection (p. 56) should be instituted. If respiratory distress is marked the patient should be propped up comfortably with pillows or a backrest.

Cough, when distressing and unproductive, should be controlled by the measures described on page 333. When secretions are present in the bronchi the patient should be firmly encouraged to cough them up, even if the effort to do so causes pleural pain. In these circumstances a mild analgesic (p. 334) and the support of a nurse's hand on the painful side of the chest may relieve the distress of coughing. Postural drainage (p. 396) may be of value if the sputum is difficult to bring up, particularly if it is copious, as in suppurative pneumonia, or when pneumonia complicates bronchiectasis.

Pleural pain should be treated with local heat and analgesics (p. 334). It is, however, dangerous to prescribe morphine if even a mild degree of ventilatory insufficiency is present, and the safest policy is not to use this drug at all in the treatment of pneumonia.

Hypoxia demands oxygen therapy (p. 330).

Delirium, which in the early stages is caused mainly by the high temperature, and later by cerebral hypoxia, may have to be controlled by sedation. The safest drugs to use are diazepam, 5-10 mg, or paraldehyde, 5-10 ml, both by intramuscular injection.

Peripheral circulatory failure occurring in the course of pneumonia is seldom reversible once it has become established. Fluid replacement with intravenous plasma or dextran, monitored by measurements of central venous pressure, is essential, and massive doses of intravenous hydrocortisone (3 g per day or more) may be of some value. The administration of pressor agents, such as metaraminol hydrogen tartrate (Aramine) by intramuscular injection or by continuous intravenous infusion, may do more harm than good.

Abscess formation. Suppurative pneumonia is not in itself a reason for any departure from standard antibiotic policy. When an abscess cavity is present, however, it must be kept empty by regular postural drainage. Medical treatment is almost invariably successful and surgical measures nowadays are seldom required. In occasional instances, however, a large abscess may have to be drained externally or residual bronchiectasis resected.

TUBERCULOSIS

Although tuberculosis is a problem of rapidly diminishing proportions in Western Europe and North America, it remains, in the words of a World Health Organisation Report, 'the most important specific communicable disease in the world'. It is by far the largest single cause of death in the developing countries, and although the death rate in Britain has fallen to an almost negligible figure, no less than 12,000 new cases of tuberculosis were notified during 1968. These are considered good and sufficient reasons for retaining in this book a detailed account of this dangerous but now eminently curable disease. It must also be borne in mind that as the disease decreases in frequency there will be a tendency for tuberculosis to be overlooked in differential diagnosis.

The Aetiology of Tuberculosis. The fact that tuberculosis is a specific infective disease was first proved by Koch's discovery of the tubercle bacillus in 1882. Tuberculosis is unlike other infections in that while many members of the population become infected in early life only a relatively small number develop clinically recognisable evidence of disease, either at the time of the first ('primary') infection or in later years. It is possible by means of the tuberculin skin sensitivity test (p. 360) to determine whether or not a person has at any time contracted a tuberculous infection. Periodic surveys of the proportion of positive tuberculin reactors in a community may thus provide a valuable long-term indication of the efficacy of the measures employed to control the disease. In Scotland, for example, the number of positive reactors amongst 13-year-old children fell from 56 per cent in 1952 to less than 5 per cent in 1972. The Heaf tuberculin test (p. 360) is commonly used to detect reactors and if low-grade reactors are accepted as positive, many children who in fact have been infected with atypical mycobacteria will have been included erroneously. The proportion infected with mammalian tubercle bacilli may thus be as low as 2 per cent.

The Mycobacteria. There are three types of tubercle bacillus mainly responsible for the disease in man:

(*a*) the *human* type—endemic in man,
(*b*) the *bovine* type—endemic in cattle.
(*c*) the *atypical* or *anonymous* mycobacteria.

In Britain, considerably less than 1 per cent of tuberculosis in man is now caused by the bovine bacillus, which is transmitted by milk. The rapid decline in this type of infection during the past 25 years is accounted for by the energetic efforts which have been made to render milk safe by pasteurisation and by increasing the number of tuberculosis-free dairy herds. All milk produced on registered farms in Britain is now safeguarded in one or both of these two ways. The atypical mycobacteria produce patterns of disease similar to those caused by human or bovine bacilli, but the disease tends to be more sluggish in progression. These infections, though rare, are important because such mycobacteria are mostly resistant to many of the drugs used in treatment and by producing low-grade sensitivity to tuberculin tend to confuse the epidemiological study of tuberculosis.

IMMUNITY AND SUSCEPTIBILITY. Entry of the tubercle bacillus into the body by the alimentary or respiratory tract is not necessarily followed by a clinical illness, the development of which is dependent on several other factors:

1. *Natural resistance.* Susceptibility to tuberculosis is not inherited in the strict sense of the word, but the fact that certain races, such as Africans and Indians, and even certain regional groups, such as the inhabitants of the Western Isles of Scotland and of Ireland, are more prone to develop tuberculosis suggests that natural resistance varies from race to race and even from region to region. The natural resistance of a community tends to rise as the period of exposure to tuberculosis increases.

2. *Acquired immunity.* The nature and effects of acquired immunity in tuberculosis are not fully understood. It has, however, been proved that if a person contracts and recovers from a primary tuberculous infection (p. 359) he is less likely to develop active tuberculosis on subsequent exposure to the tubercle bacillus than a patient who has not previously been infected. The use

of a vaccine containing an attenuated bovine bacillus (Bacille Calmette Guérin—BCG) to induce a controlled and innocuous primary infection is based on this observation.

3. *Allergy.* After the primary infection has become established the tissues react to the tubercle bacillus in a way that differs from their initial reaction. This altered response, referred to as allergy (p. 15), takes the form of hypersensitivity to tuberculin, a complex protein constituent of the tubercle bacillus, and can be recognised by the finding of a positive tuberculin reaction (p. 360). This is a cell-mediated (delayed) hypersensitivity—Type IV (p. 35).

The effect of hypersensitivity to tuberculoprotein, which is maximal during the months following the primary infection, is to fix and destroy tubercle bacilli in the tissues. It is, therefore, one of the processes which help to localise the infection at or near its point of entry, and in that sense can be regarded as a defence mechanism. On the other hand, hypersensitivity, through its power to produce caseation and liquefaction in the primary lesion and in the regional lymph nodes, may exert an unfavourable influence on the course of the disease. The fortuitous discharge into a blood vessel of the contents of a caseous lymph node leads to wide dissemination of tuberculosis to other organs and is a well recognised hazard of every severe primary infection.

4. *Massive infection and re-infection.* The gravity of a tuberculous illness bears some relationship, although not a constant one, to the size of the infection. The danger is greatest when a young child is exposed to a massive infection from an 'open' case of pulmonary tuberculosis (i.e. a patient whose sputum contains tubercle bacilli).

The degree of immunity conferred by a primary infection, which varies considerably in different individuals, affords no certain protection against re-infection, particularly the massive re-infection which results from close contact with an open case of tuberculosis.

5. *Age and Sex.* For a very long time in Europe and America, tuberculosis affected predominantly the young people in the community and especially the young female. In the past 20 years there has been a radical change in the age and sex incidence. Whereas 20 years ago, only 20 per cent of notifications came from patients over 45 years of age, nowadays 60 per cent of patients are over 45 years of age, males predominating. This change is important in case-finding.

6. *Standard of living.* The prevalence of tuberculosis diminishes as social and economic conditions improve. Poor housing with associated over-crowding increases the risk of massive infection or re-infection occurring if one of the occupants suffers from open tuberculosis. The precise role of diet is uncertain, but gross deficiency of protein and vitamins commonly found in the developing countries in Asia and Africa may be an important aetiological factor.

7. *Occupation.* Occupation has seldom any direct bearing on the prevalence of tuberculosis. A higher or lower tuberculosis rate in any particular occupation is usually determined not by the nature of the occupation itself but by the social and economic status of those who are engaged in it and by the opportunities it provides for the transmission of infection from one person to another.

8. *Conditions Affecting Individual Patients.* Diabetes mellitus, gastrectomy and congenital heart disease all predispose to the development of tuberculosis. Another predisposing factor is regular treatment with corticosteroids. Tubercu-

lous infection in such subjects responds normally to antituberculosis chemotherapy.

Pregnancy may have an unfavourable influence on the course of untreated pulmonary tuberculosis but has no adverse effect on patients under correct supervision and treatment.

The Pathology of Tuberculosis. The characteristic lesion of tuberculosis is the *tubercle*. This consists of a microscopic nodular collection of epithelioid cells surrounded by zones of lymphocytes and fibroblasts. There may be giant cells and a few bacilli in the centre. Adjacent tubercles enlarge and coalesce at an early stage, and this is followed by central necrosis or 'caseation' which may advance rapidly with widespread tissue destruction. The lesions tend to heal by fibrosis and calcification, but destructive and reparative processes frequently co-exist.

The initial 'primary' tuberculous infection usually occurs in the lung but occasionally in the tonsil or in the alimentary tract, especially the ileo-caecal region. The primary infection differs from later infections in that the primary focus in lung, tonsil or bowel is almost invariably accompanied by a caseous lesion in the regional lymph nodes, i.e. in the mediastinal, cervical or mesenteric groups respectively.

In most people the primary lesion and the associated lymph node lesion heal and calcify. In a few, healing (particularly of the lymph node lesion) is incomplete and surviving tubercle bacilli may under certain circumstances, such as a lowering of the general health or an alteration of the balance between allergy and immunity, be discharged into the blood stream. Such patients may in consequence develop tuberculous lesions elsewhere in the body. The most common sites for '*haematogenous*' *lesions* of this kind are the lungs, bones, joints and kidneys. Such lesions may develop months or even years after the primary infection.

The primary infection may in some cases fail to heal. A primary pulmonary lesion, particularly when it occurs during adolescence or early adult life, may lead to progressive pulmonary tuberculosis. A tuberculous mediastinal lymph node, in children especially, may compress a lobar or segmental bronchus (rarely a main bronchus) and produce pulmonary collapse. Occasionally the node may ulcerate through the bronchial wall and discharge caseous material into the lumen, with the production of acute tuberculous lesions in the related lobe or segment. Infection may also be carried by lymphatics from tuberculous mediastinal glands to the pleura or pericardium with the production of *tuberculous pleurisy* or *pericarditis*. Comparable complications may occur when the primary lesion is in the tonsil or gut, e.g. '*cold abscess*' of the neck or tuberculous *peritonitis*.

Rarely, a caseous tuberculous focus either at the site of the primary infection or, more commonly, in an associated lymph node ruptures into a vein and produces acute dissemination of the disease throughout the body, a condition known as *acute miliary tuberculosis*. *Tuberculous meningitis* often accompanies this condition.

Progressive pulmonary tuberculosis may develop directly from a primary lesion or it may occur later, following reactivation of an incompletely healed primary focus in the lung or as a result of haematogenous dissemination from an unhealed lymph node lesion. Alternatively it may be the result of re-infection from an outside source after the primary focus has healed completely. All these forms of pulmonary tuberculosis, although differing in pathogenesis, have similar pathological features and can be grouped together under the term *post-primary pulmonary tuberculosis.* The characteristic pathological feature of this condition is the *tuberculous cavity*, which forms when the caseated and liquefied centre of a tuberculous pulmonary lesion is discharged into a bronchus. The walls of cavities harbour large numbers of tubercle bacilli, and the persistence of cavitation, which is determined chiefly by mechanical circumstances, is the most important single factor preventing recovery from the disease. There is, however, a strong tendency for the lesions to be localised by fibrous tissue, and provided that gross cavitation is not present the disease is frequently self-limiting, although complete healing by fibrosis and calcification is a slow process. Extension of the disease to other parts of the same lung or to the opposite lung is a common consequence of cavitation and is caused either by direct spread of the disease or by aspiration, via the bronchi, of infected secretions from the cavity.

Extension of the infection to the pleura either by direct or lymphatic spread causes *tuberculous pleurisy*, which is sometimes accompanied by effusion and is occasionally followed by the development of a *tuberculous empyema.* Blood-borne dissemination to other organs of the body is uncommon in post-primary pulmonary tuberculosis.

Clinical Features. There are two groups of clinical features in tuberculosis:

1. Those due to the systemic effects of the disease, which include lassitude and malaise, impairment of appetite, loss of weight, anaemia, sweating especially during sleep, pyrexia and tachycardia. The pyrexia is usually most marked in the late afternoon or evening and sometimes occurs only at these times. The absence of constitutional symptoms does not necessarily mean that the disease is inactive.

2. Those caused by the local effects of the tuberculous lesions, which are summarised below according to anatomical site.

Lungs and bronchi: cough, sputum, haemoptysis, dyspnoea.
Pleura: pleural pain, dyspnoea due to pleural effusion.
Larynx: hoarseness, with dysphagia at a later stage from involvement of pharynx.
Tongue: ulceration (rare).
Intestine: diarrhoea, malabsorption or intestinal obstruction.
Peritoneum: ascites, attacks of intestinal obstruction due to plastic peritonitis.
Pericardium: pericardial effusion, constrictive pericarditis later.
Kidneys and bladder: haematuria, increased frequency of micturition. (These are relatively late developments, early renal lesions being symptomless.)
Epididymo-orchitis: painless swelling, sinus formation later.
Fallopian tubes: infertility, tubal abscess.
Brain: tuberculoma with or without focal neurological signs.
Meninges: symptoms and signs of meningitis.

Lymph nodes: enlargement of nodes, often with 'cold' abscess and sinus formation later.
Adrenal glands: symptoms and signs of Addison's disease.
Bones and joints: osteitis, synovitis, 'cold' abscesses.
Skin: lupus vulgaris, erythema nodosum.
Eyes: phlyctenular keratoconjunctivitis, iridocyclitis, choroiditis.

In the sections which follow an account is given of those manifestations of tuberculosis which involve the lungs, namely primary pulmonary tuberculosis, acute miliary tuberculosis and post-primary pulmonary tuberculosis. Tuberculous pleurisy is described on page 414. For information regarding other manifestations of tuberculosis the reader should refer to the appropriate sections of the book. The treatment and prevention of tuberculosis are dealt with on pages 366-372.

Primary Pulmonary Tuberculosis

The pathological features of this type of tuberculosis have already been described (p. 357). The primary infection usually occurs in childhood but is sometimes delayed until adult life. A history of contact with a case of active pulmonary tuberculosis is obtained in many instances.

Clinical Features

1. In the vast majority of cases the primary infection produces no symptoms or signs and passes unnoticed unless routine radiological examination of the chest happens to be carried out at the appropriate time or serial tuberculin tests show conversion from negative to positive. Such close observation is seldom undertaken unless there is a particular liability to tuberculous infection, e.g. in children or nurses exposed to open cases of tuberculosis.

2. In a few cases the primary infection produces a febrile illness. It is generally mild and lasts for no more than 7 to 14 days, but it may be accompanied by other systemic features of tuberculous infection. It is unusual for gross focal symptoms or signs to develop in an uncomplicated case, but a slight dry cough is occasionally present. The leucocyte count is usually normal but the erythrocyte sedimentation rate is invariably raised.

3. The primary infection may be accompanied by *erythema nodosum.* This condition is characterised by bluish-red, raised, tender cutaneous lesions on the shins and, less commonly, on the thighs, and is associated in some cases with pyrexia and polyarthralgia. The lesions of erythema nodosum do not exhibit the histological features of tuberculosis and tubercle bacilli cannot be isolated from them. They are thus assumed to be non-specific focal manifestations of allergy. Erythema nodosum may, however, be the first clinical indication of a tuberculous infection. In such cases the tuberculin reaction (below) is always strongly positive and evidence of primary tuberculosis can usually be detected on the chest radiograph.

Erythema nodosum may be seen in conditions other than primary tuberculosis, e.g. sarcoidosis, streptococcal infections and, rarely, following the administration of a sulphonamide drug. It may also occur as an isolated phenomenon without apparent cause. In countries where tuberculosis is no longer prevalent, sarcoidosis (p. 409) is the condition with which erythema nodosum is most frequently associated. In such cases the tuberculin reaction is negative or only weakly positive and the chest radiograph usually shows *bilateral* enlargement of the hilar lymph nodes without at this stage any pulmonary abnormalities.

4. Occasionally the primary pulmonary infection pursues a progressive course (p. 357). Symptoms and signs due to its complications may appear either during the course of the initial illness or after a latent interval of weeks or months. Such complications include dry pleurisy or pleural effusion (p. 416), lobar or segmental collapse (p. 396), acute miliary tuberculosis (p. 361), tuberculous meningitis (p. 857), and post-primary pulmonary tuberculosis (p. 362).

Diagnosis. The three most valuable diagnostic investigations in primary pulmonary tuberculosis are:

1. *Radiological examination of the chest.* In children this usually shows unilateral enlargement of the hilar lymph nodes and demonstrates the primary intrapulmonary lesion if it is large enough to be visible radiologically. In adolescents and young adults the lymph node component of the primary complex is usually less conspicuous than in children and the pulmonary lesion more prominent. Complications such as pleural effusion, collapse and acute pneumonic tuberculosis may be superimposed.

2. *Tuberculin test.* With the Mantoux technique a solution of Old Tuberculin or purified protein derivative (PPD) tuberculin is injected intradermally on the flexor aspect of the forearm. The test is regarded as positive if, two to four days after injection, there is a reaction consisting of a raised area of inflammatory oedema not less than 5 mm in diameter, with surrounding erythema. The test is regarded as negative if there is no reaction or if there is an immediate (non-specific) reaction which disappears completely within 48 hours. The test should first be carried out with 1 tuberculin unit (TU) in 0·1 ml of normal saline. If there is no reaction it should be repeated with 10 TU in the same volume of saline. In order to obtain accurate results it is essential to use freshly prepared dilutions of tuberculin.

Differential tuberculin testing with antigens prepared from other mycobacteria, e.g. PPD-A (*M. avium*) or PPD-Y (*M. kansasii*) is often a satisfactory method of distinguishing atypical mycobacterial infection from tuberculosis.

The significance of the tuberculin test in relation to tuberculous infection has already been discussed (p. 356). The younger the patient the greater the diagnostic significance of a positive test. A repeatedly negative test over a period of six weeks from the onset of symptoms practically rules out a diagnosis of tuberculosis except in the elderly, after acute exanthemata, and in severe miliary tuberculosis and tuberculous meningitis.

Tuberculin testing is an essential part of the examination of the family contacts of cases of tuberculosis. Apart from its value as a diagnostic measure it indicates which of the contacts should be vaccinated with BCG. When large numbers are being tested, particularly children, the *Heaf multiple puncture tuberculin test* is preferable to the Mantoux technique as it is more rapidly performed and is less painful. For this test a solution containing 100,000 TU of PPD tuberculin per ml, to which adrenaline has been added, should be used.

These tests may be read from the third to the seventh day and four grades of positivity are recognised.

Grade I—At least four discrete papules.
II—The papules coalesce to form a ring.
III—The area encircled by the papules is completely indurated.
IV—Any reaction which is greater than III, including central necrosis.

Reaction in grades III and IV indicates infection with mammalian tubercle bacilli and a grade I reaction usually indicates infection with atypical tubercle bacilli. The significance of a grade II reaction is uncertain. The *tuberculin tine test* is carried out by a disposable unit carrying four prongs or 'tines' 2 mm in length mounted on a disc, the tines having been coated with Old Tuberculin.

3. *Bacteriological examination.* Sputum is seldom available in cases of primary pulmonary tuberculosis, but tubercle bacilli can sometimes be isolated by culture of fasting gastric juice or of secretion obtained by swabbing the larynx. At least three specimens should be examined. The isolation of tubercle bacilli is absolute proof of the diagnosis, but a negative result does not exclude it.

Primary pulmonary tuberculosis must be distinguished from other febrile illnesses such as influenza and infectious mononucleosis, from acute respiratory infections such as acute bronchitis and pneumonia, and from other causes of hilar lymph node enlargement such as the reticuloses (p. 753) and sarcoidosis (p. 409).

Prognosis. Since primary pulmonary tuberculosis and its complications respond satisfactorily to antituberculosis chemotherapy (p. 366), which should be given in every case, the prognosis is excellent.

Acute Miliary Tuberculosis

The pathogenesis of this condition has already been discussed. Hitherto it has occurred chiefly in children and young adults. With the changing age-structure of tuberculosis in many countries it is now affecting persons in older age-groups in whom it takes the form of an insidious illness—the so-called 'cryptic' type—which is often difficult to diagnose. Before the introduction of streptomycin and isoniazid the disease was invariably fatal but most cases now recover completely.

Clinical Features. The disease may start suddenly or may be preceded by a few weeks of vague ill-health. In children and young adults the systemic disturbance rapidly becomes profound. In particular there is high remittent or intermittent pyrexia with drenching sweats during sleep, marked tachycardia, loss of weight and usually progressive anaemia. Cough and dyspnoea are occasionally present. There may be no abnormal physical signs in the lungs, although widespread fine crepitations are not infrequently heard at some stage of the disease. The liver is often enlarged and the spleen often palpable and sometimes tender. Choroidal tubercles may be visible in the fundus on ophthalmoscopy but are rarely present in miliary disease affecting the elderly. Leucocytosis is usually absent or slight and the erythrocyte sedimentation rate variable. If chemotherapy is not given the patient's condition deteriorates rapidly and death takes place from exhaustion or from tuberculous meningitis within four to eight weeks.

The 'cryptic' form of the disease occurs in older age-groups, particularly females. General malaise and eventual exhaustion, loss of weight, and anaemia are common presenting features. Respiratory symptoms are rare, and the characteristic miliary shadows are often absent. Choroidal tubercles are rarely observed in this form of the disease. A variety of specific blood disorders—neutropenia, pancytopenia and leukaemoid reaction—may be found. The clinical features are often so non-specific that the diagnosis is frequently made only at autopsy.

Diagnosis. The clinical diagnosis of acute miliary tuberculosis can be made with certainty only when radiological examination of the chest shows the characteristic fine, 'miliary' mottling symmetrically distributed throughout both lung fields or when choroidal tubercles are seen. These changes take a few weeks to develop but the diagnosis can often be suspected at an earlier stage by the symptoms, fever, progressive clinical deterioration, persistent pyrexia and splenomegaly. Bacteriological confirmation should be sought by culture of sputum, urine or bone-marrow. In difficult cases, liver biopsy may be diagnostic. Although the tuberculin reaction (p. 360) is usually positive, a negative result does not always exclude acute miliary tuberculosis, as tuberculin sensitivity is occasionally depressed in the acute phase of the illness. In 'cryptic' cases, a therapeutic test of chemotherapy with ethambutol and isoniazid (p. 367) is essential as death is inevitable if treatment is not given.

Acute miliary tuberculosis must be distinguished from other causes of severe pyrexia without obvious localising symptoms or signs, such as enteric fever (p. 69), infective endocarditis (p. 263), staphylococcal septicaemia (p. 63), empyema (p. 418), subphrenic abscess (p. 505), acute pulmonary tuberculosis (below) and the reticuloses (p. 753).

Prognosis. Antituberculosis chemotherapy (p. 366) has reduced the mortality of miliary tuberculosis from 100 per cent to less than 5 per cent. The cause of death is often tuberculous meningitis, although many patients who develop this complication make a complete recovery, provided there has been no delay in starting treatment.

Post-primary Pulmonary Tuberculosis

Most of the morbidity and mortality from tuberculosis is caused by this form of the disease. Although in underdeveloped countries it is most prevalent in adolescence and early adult life, the majority of cases in Western Europe and North America now occur in middle-aged and elderly subjects, particularly males.

The nature of the pathological lesions has already been described (p. 357). They are most frequently situated in the upper lobes. Another common site is the apex of a lower lobe. The disease is often bilateral; usually it starts in one lung and spreads via the bronchi to the other; less commonly it develops in both lungs at the same time. Occasionally, when the disease takes an acute form, the initial lesion is pneumonic or bronchopneumonic.

Clinical Features. The onset of post-primary pulmonary tuberculosis is usually insidious, with the gradual development of general symptoms or of cough and sputum. Sometimes a dramatic incident such as a haemoptysis, an attack of pleurisy or a spontaneous pneumothorax marks the onset of the disease, but the diagnosis is now frequently made by mass radiography before any symptoms have appeared.

The local respiratory symptoms which may occur during the course of post-primary pulmonary tuberculosis are:

1. *Cough*, which may be one of the earliest symptoms or which may not be troublesome until a late stage. Its absence does *not* exclude a diagnosis of pulmonary tuberculosis.
2. *Sputum*, which, like cough, may not become a prominent feature until the disease has reached an advanced stage. It is usually mucoid at first but later becomes purulent. It is rarely foetid.
3. *Haemoptysis*. In the early stages it is due to the erosion of a small vessel in a caseating lesion and the bleeding is usually slight. In the late stages it originates from a large vessel in the wall of a cavity and the haemorrhage may be large, occasionally fatal.
4. *Dyspnoea on exertion*, which is usually a late symptom, but may develop acutely when due to a spontaneous pneumothorax or to a rapidly developing pleural effusion.
5. *Pleural pain*, which is usually due to dry pleurisy but occasionally to spontaneous pneumothorax.

PHYSICAL SIGNS IN THE CHEST. In the early stages no abnormal physical signs may be elicited, but, despite this, an extensive lesion may be visible radiologically. The earliest physical signs consist of a few medium or coarse crepitations, usually situated over one or other lung apex posteriorly. These crepitations may be present only after coughing.

As the disease advances the percussion note over the site of the lesion loses its normal resonance and there is a change in the character of the breath sounds, which may become either diminished in intensity or harsh vesicular with prolonged expiration. The crepitations become more numerous and more coarse. Ultimately the physical signs of consolidation, cavitation and fibrosis may appear (p. 326).

Pleurisy, with or without effusion, and spontaneous pneumothorax may modify the pulmonary signs.

Radiological Examination. This is of paramount importance for diagnosis in the early stages before physical signs appear and for assessment of the extent and progress of the disease. The earliest radiological change is an ill-defined opacity or opacities, usually situated in one of the upper lobes. In more advanced cases the opacities are larger and more widespread, and may be bilateral. Occasionally there is a dense, homogeneous shadow involving a whole lobe ('pneumonic tuberculosis').

An area or areas of translucency within the opacities indicates cavitation. Very large cavities may be visible in some cases. If there is progress towards healing the opacities shrink, become more clearly defined, and may later show calcification. When fibrosis is marked the trachea and heart shadow are displaced towards the side of the lesion.

In any case of tuberculosis it is common for lesions at different stages of development to co-exist. Thus in one area there may be cavitation, in a second evidence of fibrosis and in a third an opacity due to recent disease.

The presence of cavitation in an untreated case usually indicates that the disease is active. When cavitation is absent, however, it may sometimes be difficult to assess the activity of a tuberculous lesion from a single radiograph. Observation of the lesion over a period of time will be necessary in doubtful cases.

The radiological appearances of pleural effusion and pneumothorax, which may accompany those of pulmonary tuberculosis, are described on pages 415 and 423.

Diagnosis. The general principles governing the diagnosis of tuberculosis have already been stated (p. 360). The grounds on which pulmonary tuberculosis should be suspected are:

1. Unexplained cough persisting for more than three weeks.
2. Haemoptysis.
3. Pleural pain not associated with an acute illness.
4. Spontaneous pneumothorax (although most cases are *not* tuberculous).
5. Unexplained tiredness or loss of weight, even in the absence of respiratory symptoms.

The presence of any of these symptoms demands immediate radiological examination of the lungs and, if any abnormality is found, the examination of at least three specimens of sputum for tubercle bacilli.

When bacilli are numerous, the diagnosis can readily be made by microscopical examination of sputum smears stained by the Ziehl-Neelsen method, but culture of sputum (or of fasting gastric juice or laryngeal swabs, if no sputum can be obtained) is essential for the isolation of bacilli present in small numbers and for the detection of drug resistance (p. 44). Cultural methods are thus of great practical value and should be used in the examination of every specimen, if facilities permit.

The conditions with which pulmonary tuberculosis may be confused include pneumonia (p. 341), bronchial carcinoma (p. 401), bronchiectasis (p. 393), chronic bronchitis (p. 387), infective endocarditis (p. 263), diabetes mellitus (p. 675) and thyrotoxicosis (p. 631).

In the vast majority of cases the diagnosis of pulmonary tuberculosis can be made with certainty by radiological examination of the chest, bacteriological examination of the sputum for tubercle bacilli, or a combination of the two. In some cases it is necessary to carry out further radiological examination after a course of penicillin in order to exclude an acute inflammatory cause for an abnormal shadow.

Pulmonary tuberculosis must be regarded as active and requiring treatment if one or more of the following features is present:

1. Local or general symptoms, particularly haemoptysis or pleural pain.
2. A radiological opacity known or suspected to be of recent development, or one which has increased in extent during a period of observation.
3. Radiological evidence of cavitation.
4. Tubercle bacilli in sputum, gastric juice, or laryngeal swabs.

Complications

1. *Pleurisy with or without effusion.* This common complication is described on pages 414-416.

2. *Spontaneous pneumothorax.* This may be due to rupture of a tuberculous lesion into the pleural space (p. 421).

3. *Tuberculous empyema or pyopneumothorax* (p. 419). This may complicate spontaneous pneumothorax.

4. *Tuberculous laryngitis.* This usually occurs as a complication of advanced pulmonary disease.

5. *Tuberculous enteritis.* This is practically confined to advanced cases. It is due to the swallowing of heavily infected sputum.

6. *Ischio-rectal abscess and fistula-in-ano.* The abscess forms as a result of tubercle bacilli passing through an abrasion in the rectal mucosa. Secondary pyogenic infection invariably occurs, and a fistula may form when the abscess is incised or if it ruptures spontaneously.

7. *Dissemination of tuberculosis via the blood stream* is very unusual in post-primary pulmonary tuberculosis, but may occur in advanced cases with the production of renal tuberculosis or tuberculous meningitis.

8. *Ventilatory failure* (p. 323) and *right ventricular failure* (p. 246) are important complications if extensive areas of late tissue are destroyed by tuberculosis. Although the tuberculous infection itself can be controlled, the residual pulmonary damage and the fibrosis and emphysema with which it is invariably associated may leave the patient seriously disabled by exertional dyspnoea.

9. *Secondary infection* of a healed cavity with fungi such as *Aspergillus fumigatus* (p. 372) may lead to chronic ill-health. Occasionally the rupture of a large blood vessel in the wall of a pulmonary cavity or a dilated bronchus may result in a massive or even fatal haemoptysis long after the tuberculous infection has been eradicated.

Prognosis. With the advent of effective chemotherapy there has been a remarkable decline in the mortality from pulmonary tuberculosis. Provided the tubercle bacilli are not initially drug-resistant and chemotherapy is used correctly, a fatal outcome is extremely uncommon, even if the disease has reached an advanced stage when it is first recognised. The advent of new effective anti-tuberculosis drugs has also improved the outlook for those patients whose bacilli are resistant to two or three of the standard drugs. The serious late complications of ventilatory failure and secondary infection with pyogenic bacteria or fungi can all be prevented if pulmonary tuberculosis is diagnosed at a reasonably early stage and is efficiently treated.

The Treatment of Tuberculosis

General Principles

1. *Antituberculosis chemotherapy* is by far the most important measure in the treatment of all forms of tuberculosis and should be given to every patient with active disease.

2. *Rest* is unimportant except in a few specific circumstances. The current practice is to keep patients in bed only until acute symptoms have subsided. The majority of patients are ambulant throughout treatment, many of them remaining at work. Immobilisation is of course necessary in certain forms of skeletal tuberculosis.

3. *Isolation* of patients who are excreting tubercle bacilli and who are therefore potentially infectious has always been an important principle. The observation made in Madras that the frequency of disease amongst contacts was no greater whether the patient was treated at home or in a sanatorium has led to the adoption of a policy whereby patients, even those who are sputum-positive on microscopy, are treated wholly as out-patients. However, many authorities still prefer to isolate patients from contact with young children. Hospitalisation for an initial period of treatment as distinct from isolation may be recommended for patients who cannot be relied upon to adhere to the regimen advised and for patients with difficult therapeutic problems.

4. *Surgical treatment* such as pulmonary resection, nephrectomy or removal of superficial lymph nodes is now rarely required. However, an irreparably damaged kidney should be removed and drainage of an abscess from tuberculous lymph nodes or of an empyema may be necessary.

Chemotherapy

Apart from a few minor variations in dosage and duration of treatment (p. 368) the policy governing the use of antituberculosis drugs is the same for all manifestations of the disease.

Drugs. In the United Kingdom, five drugs—streptomycin, sodium aminosalicylate (PAS), isoniazid, ethambutol and rifampicin—should be considered in initial treatment of tuberculosis. A sixth drug, thiacetazone, is widely used in developing countries.

Because in the past chemotherapy was often used incorrectly by present standards, the sputum of some patients with chronic pulmonary tuberculosis contains drug-resistant tubercle bacilli. Infection from these sources gives rise to initial primary drug resistance in a small proportion of patients—less than 4 per cent in Britain. Because of the risk of initial drug resistance, treatment should be commenced with 3 drugs.

The selection of a suitable combination of drugs for a patient with tuberculosis depends on many different factors, such as the results of *in vitro* sensitivity tests, the nature of any previous chemotherapy and the risk of side-effects. It is also necessary to consider in what form the treatment can be most conveniently and reliably administered. Cost is an important factor especially in developing countries. Although in most cases drugs which can be given by mouth are to be preferred, particularly for out-patient treatment, it may be necessary to employ methods whereby patients who cannot be trusted to take antituberculosis chemotherapy regularly are given one drug (streptomycin) by injection while the whole daily dose of a second drug (e.g. isoniazid) is administered by mouth at the same time under strict supervision.

When the diagnosis is first made, information regarding the drug sensitivity of the tubercle bacillus is not usually available as the results of *in vitro* sensitivity tests are not obtainable for about 12 weeks. Treatment cannot be deferred for this length of time, and a combination of drugs must therefore be selected which takes into account the possibility of infection with a drug-resistant organism.

Phases of Treatment. Treatment is given in two phases, an initial intensive phase and a continuation phase.

1. INITIAL INTENSIVE PHASE. Ideally, all newly diagnosed patients should be treated with three drugs for an initial period of 12 weeks. In minimal disease, four weeks may be sufficient. Highly effective regimens are:

Isoniazid *plus* streptomycin *plus* ethambutol *or* rifampicin *or* PAS (sodium salt)

in the doses detailed below. Ethambutol and rifampicin are much more readily accepted by patients than PAS, but are more costly. PAS is well tolerated by very young children in whom it is to be preferred to ethambutol because of the difficulty in assessing ocular toxicity in this age group. Rifampicin may be substituted for streptomycin. The drugs should be used in the following once daily doses:

Isoniazid	Children	3 mg/kg
	Adults	200-300 mg
	Intermittent regimen	15 mg/kg†
	Miliary	10-15 mg/kg
Streptomycin sulphate	Children	30 mg/kg
	Adults under 40 years and weighing more than 45 kg	1 g
	Adults 40-60 years or weighing less than 45 kg	0·75 g
	Adults over 60 years or in cases with renal failure	According to serum levels
*Ethambutol		15 mg/kg
Rifampicin	Children	10-20 mg/kg
	Adults	10 mg/kg (maximum 600 mg)
*Sodium amino-salicylate (PAS)	Children	300 mg/kg
	Adults	10-12 g

* In cases of renal failure the doses of ethambutol and PAS given may also need to be determined according to serum levels.

† Plus pyridoxine 10 mg.

2. CONTINUATION PHASE. In this phase, either an unsupervised oral or a fully supervised regimen may be selected. Oral regimens include a combination of isoniazid with ethambutol, rifampicin or PAS. Isoniazid and ethambutol may be prescribed together (*Mynah*) and isoniazid and PAS are dispensed together in the following forms:

Sodium Aminosalicylate and Isoniazid Cachets, N.F., 4 cachets twice daily.
Pycasix (Smith and Nephew) or Pasinah 6PH (Wander), 3 cachets twice daily.
Inapasade S.Q. (Smith and Nephew), 1 packet daily.

Alternatively a supervised regimen may be given twice weekly at 3- and 4-day intervals in the following doses:

Streptomycin sulphate 1 g by intramuscular injection
Isoniazid 15 mg/kg body weight by mouth
Pyridoxine 10 mg to prevent peripheral neuropathy.

This type of chemotherapy is particularly valuable for unco-operative patients, as treatment can be wholly supervised, the tablets being administered at the same time as the injections.

Inexpensive Treatment Regimens. In the underdeveloped countries it will usually be impossible for economic reasons to adhere to the recommended chemotherapeutic regimens. The following inexpensive forms of treatment are reasonably effective if administered for 12 months:

(*a*) Streptomycin (1 g) by intramuscular injection *plus* isoniazid (15 mg/kg) by mouth plus pyridoxine (10 mg) on two days per week. This is 90 to 95 per cent effective: if one, or preferably two months of treatment with all three standard drugs can be afforded as initial treatment, the effectiveness of this regimen is nearly 100 per cent.

(*b*) Isoniazid (300 mg) plus thiacetazone (150 mg) given in a single daily dose by mouth is extremely cheap, and is about 80 to 85 per cent effective.

Side-effects. In choosing a suitable drug regimen for individual patients it is important to bear in mind those side-effects which are particularly liable to cause serious chronic disability, such as vestibular disturbance due to streptomycin and optic neuritis due to ethambutol. Streptomycin must be prescribed with caution in the middle-aged and elderly, who find difficulty in compensating for vestibular disturbance. Even in the relatively low dose recommended for ethambutol, a few patients develop optic neuritis and a proportion of them are left with a permanent visual defect. This potential hazard must be taken into consideration whenever ethambutol is prescribed. Patients should be instructed to test their own visual acuity daily.

Streptomycin and PAS, and occasionally isoniazid, ethambutol and rifampicin, may produce a reaction of hypersensitivity, consisting of pyrexia and an erythematous skin eruption, which usually develops two to four weeks after treatment is started. If this occurs the patient may be desensitised by giving small but increasing doses of the drug until the full dose is tolerated. Occasionally the hypersensitivity is so severe that corticosteroids have to be used to control it and to allow desensitisation to be undertaken. If this proves difficult desensitisation should be abandoned and an alternative effective drug substituted.

Other side-effects include:

Streptomycin: deafness (rare).
PAS: anorexia, nausea, vomiting, diarrhoea (common); goitre and hypothyroidism (rare); hepatitis, usually associated with hypersensitivity (rare); intestinal malabsorption (rare); hypokalaemia (rare); haemolytic anaemia (rare).
Isoniazid: polyneuropathy (rare); lack of mental concentration (rare).
Rifampicin: hepatitis (rare); purpura (rare); fever, respiratory, cutaneous and abdominal syndromes (intermittent regimens only).
Thiacetazone: nausea, vomiting, anaemia (rare); leucopenia (rare).

Response to Treatment. If the bacilli at the start of treatment are fully sensitive to the drugs in use it is most unusual, even in advanced cases, for cultures of sputum, gastric washings, laryngeal swabs or urine to remain positive for longer than six months. Where facilities for sensitivity testing do not exist, reliance must be placed on smear examination.

Persistence of a positive sputum after six months' treatment suggests that drug resistance has occurred. Alternatively, failure may have been due to irregular treatment. Chemical tests to detect the presence of PAS, isoniazid and rifampicin in urine are available. Rifampicin gives a pink colour to urine and sweat.

Duration of Treatment. The recommended duration of treatment for many years has been 12 months for primary lesions, miliary tuberculosis, pleural effusions and minimal pulmonary tuberculosis; 18 months for advanced pulmonary tuberculosis and for genito-urinary lymph node and skeletal tuberculosis. With the advent of rifampicin shorter periods of treatment may be possible in the future, but this has still to be proved.

Drug-resistant Tubercle Bacilli. The treatment of patients infected with drug-resistant tubercle bacilli presents a problem requiring specialised knowledge for its solution. Additional drugs available for the treatment of such cases are:

Capreomycin	0·75-1 g	intramuscularly
Ethionamide	0·75-1 g	given in a single oral dose daily.
Prothionamide	0·75-1 g	
Pyrazinamide	20 mg/kg	
Cycloserine	0·75-1 g	

Corticosteroid Drugs

These agents suppress the inflammatory reaction excited by the tubercle bacillus and by interfering with tissue defence mechanisms may promote a rapid dissemination of infection throughout the body. If, however, a corticosteroid drug is given in conjunction with effective antituberculosis chemotherapy it may exert a *favourable* influence on the course of the disease by reducing the severity both of the local inflammatory reaction and of the associated systemic disturbance. In acute cases of pulmonary tuberculosis such treatment will rapidly relieve pyrexia, and will often produce a dramatic improvement in the radiological appearances. The effect is temporary and ceases when the corticosteroid drug is withdrawn, but it may save the lives of patients with fulminating tuberculous infection by permitting them to survive until antituberculosis chemotherapy has had time to exert its influence. Prednisolone, the drug most frequently used in these cases, is given in a dose of 15-20 mg daily for about three months.

Corticosteroid drugs in combination with chemotherapy may also be of value in tuberculous pleural and pericardial effusion, tuberculous disease of intrathoracic or superficial lymph nodes, tuberculosis involving the eye and particularly in tuberculous meningitis.

Symptomatic Treatment

(*a*) *Cough* (p. 333).

(*b*) *Haemoptysis*. A sedative may be given to allay anxiety, e.g. diazepam, 5-10 mg, thrice daily. Morphine, which depresses the cough reflex, may have the effect of allowing blood clot to accumulate in the bronchi and should seldom be prescribed. Haemoptysis nearly always stops spontaneously, and firm reassurance to this effect lessens the strains of what, to the patient and his relatives, is a most alarming experience.

If the haemorrhage is very severe a blood transfusion should be given and, if respiratory obstruction develops, the blood must be removed from the bronchi by aspiration through a bronchoscope. Control of the bleeding by surgical measures is occasionally required.

(*c*) *Pain in the Chest*. The treatment of pain due to dry pleurisy or spontaneous pneumothorax has been described on page 334.

(*d*) *Fever and sweating*. These symptoms usually subside soon after chemotherapy is started. When persistent and excessive they should be treated by repeated tepid sponging.

(*e*) *Hoarseness*. Hoarseness is usually due to tuberculous laryngitis, which responds rapidly to specific chemotherapy provided the organism is not drug-resistant.

(*f*) *Diarrhoea*. Severe and continued diarrhoea in a patient with pulmonary tuberculosis is usually due to tuberculous enteritis. In most cases it can be rapidly controlled by chemotherapy. It must be remembered, however, that diarrhoea may also be caused by PAS.

The Prevention of Tuberculosis

A great deal has already been achieved in the control of tuberculosis, but much remains to be done. Control programmes must be adapted to the needs of the community and are often limited by financial allocations.

1. **Raising the Resistance of the Population to the Disease** by:

(*a*) *Good social conditions*, including satisfactory housing and an adequate diet—tuberculosis recedes as socio-economic conditions improve.

(*b*) *BCG* (*Bacille Calmette Guérin*) *Vaccination.* BCG vaccination is usually performed by intracutaneous injection of 0·1 ml of the vaccine. Multiple puncture vaccination is practised in some areas. If a papule develops at the site of vaccination this is now taken as evidence of successful vaccination. In adolescents an effective vaccine has been shown to give a level of protection of 80 per cent. The precise duration of protection is unknown but is probably in the range of three to seven years. The place of vaccination in any control programme varies according to the epidemiological situation. In countries where the disease is endemic, mass vaccination of the new-born and of whole communities without preliminary tuberculin-testing may be advisable. In Britain BCG vaccination is offered to contacts of infectious cases, to personnel such as workers in hospital with a high risk of exposure to infection and to 13-year-old children who are tuberculin-negative. In areas where the disease is comparatively rare, vaccination of the adolescent is unnecessary. In these communities the tuberculin test is a very valuable diagnostic and epidemiological tool.

2. **Reduction of the Incidence of Human Infection** by:

(*a*) *The detection and isolation of the maximum number of cases*, if possible before tubercle bacilli are present in the sputum. Mass radiography is obviously important in case-finding: priority must be given to examination of persons most likely to be suffering from the disease, to those who would be particularly liable to infect others, e.g. teachers, nurses, hairdressers and bus conductors, and to those groups with a high incidence of tuberculous infection such as inhabitants of lodging houses, mental hospitals and prisons. The highest yield of all is from persons referred by family doctors on account of suspicious symptoms. The provision of easy access to radiological services for such groups is still necessary. Examination of contacts should always be carried out, tuberculin-testing and radiographic facilities being provided by the chest clinic. Isolation where appropriate and effective treatment of patients are obvious means of contributing to the elimination of tuberculosis. Microscopic examination of sputum is a simple and less expensive method of detecting infectious patients than mass radiography and is especially useful in under-developed countries.

(*b*) *Chemoprophylaxis* in tuberculosis is a relatively new concept. The administration of drugs to whole communities to prevent infection or to prevent persons who have been infected from developing clinical disease is not recommended. However, selective chemoprophylaxis of the infected person particularly susceptible to the development of disease is an important control measure. Examples of such persons are children under five years of age (because of the risk of meningitis), persons who have recently undergone tuberculin conversion and adolescents with very strongly positive tuberculin reactions.

3. **The Elimination of Tuberculous Infection in Milk.** Tuberculosis in dairy cattle has been virtually eradicated in Britain and as, in addition, most of the milk on sale is now pasteurised, bovine tuberculosis in man has almost completely disappeared. Pasteurisation kills the tubercle bacillus by heat while preserving the nutritive components of the milk with the exception of vitamin C. It also sterilises milk infected with pathogenic organisms such as streptococci, typhoid

bacilli and *Brucella abortus*. Unpasteurised milk produced under strictly controlled hygienic conditions ('Certified' or 'Tuberculin-tested') is still obtainable but is more expensive than ordinary pasteurised milk and potentially less safe.

RESPIRATORY DISEASES CAUSED BY FUNGI

Most fungi encountered by man are harmless saprophytes, but some species may in certain circumstances infect human tissues or promote damaging allergic reactions.

The term *mycosis* is applied to disease caused by fungal infection. Systemic factors which predispose to fungal infection include metabolic disorders, such as diabetes mellitus, toxic states such as chronic alcoholism, diseases such as leukaemia and myelomatosis in which immunological responses are disturbed, and treatment with agents, such as corticosteroids, immunosuppressive drugs and deep X-rays, which impair the body's defences against infection. Local factors, such as tissue damage by suppuration or necrosis and the elimination of the competitive influence of a normal bacterial flora by antibiotics, may also facilitate fungal infection.

Aspergillosis. This is the most common respiratory mycosis in Britain. Inhaled air-borne spores of *Aspergillus fumigatus* lodge and germinate in pulmonary cysts or bullae, 'healed' tuberculous cavities (p. 365), dilated bronchi, lung abscesses or pulmonary infarcts. In most cases the fungal infection remains localised to the site of the original lesion, but occasionally, when resistance is low, it may extend into adjacent normal lung tissue, or via the bronchi into the opposite lung, with the production of extensive pulmonary necrosis and grave systemic disturbance (necrotising pulmonary aspergillosis).

When a pre-existing pulmonary cavity is infected by *A. fumigatus*, a large spherical mass of fungal mycelium may form within the cavity, producing on X-ray examination a tumour-like opacity to which the term *mycetoma* or *aspergilloma* is applied. This type of lesion can readily be distinguished from a peripheral bronchial carcinoma by the presence of a crescent of air between the mycelial mass and the cavity wall. An aspergilloma usually produces no specific symptoms, but is occasionally responsible for recurrent haemoptysis.

Whenever mycelium is present in large quantities in a pulmonary cavity, or in any other lesion, precipitating antibodies can be detected in the serum by means of a gel diffusion test, using an antigen derived from *A. fumigatus*. This test is of considerable diagnostic value.

Candidosis. *Candida albicans* is a normal commensal of the skin and alimentary tract, but may multiply, and produce superficial mycotic lesions, when the bacterial flora is suppressed by antibiotics. Buccal candidosis or 'thrush' is a common condition in these circumstances. Occasionally, in debilitated subjects, the lesions extend downwards into the respiratory tract, with the production of bronchial or pulmonary candidosis.

Other Pulmonary Mycoses. Other mycoses which may involve the lungs, all of which are rare, include nocardiosis (*Nocardia asteroides*), cryptococcosis

(*Cryptococcus neoformans*), mucormycosis (*Mucorales* spp.), blastomycosis (*Blastomyces dermatitidis*), and sporotrichosis (*Sporotrichum schenekii*). Only the first three of these conditions have been encountered in Britain. In a somewhat different category are histoplasmosis (*Histoplasma capsulatum*) and coccidioidomycosis (*Coccidioides immitis*), which are endemic in certain areas of North America and Africa, and produce local or systemic granulomatous lesions resembling tuberculosis.

Diagnosis and Treatment

The diagnosis of a pulmonary mycosis is usually made by mycological examination of the sputum, supported by serological tests for precipitating antibodies, and in some instances by skin sensitivity tests.

Treatment of the pulmonary mycoses is difficult and unsatisfactory. The administration of antibacterial drugs should be stopped, and antifungal agents substituted. Nystatin and natamycin by inhalation may control the more superficial respiratory mycoses involving the trachea and bronchi. For grave pulmonary infections amphotericin B, a potent but highly toxic antifungal agent, may have to be given intravenously in a dose of 0·25 mg per kg body weight on alternate days, increasing gradually to 1 mg per kg over the course of one to two weeks if side-effects permit. Surgical resection of a mycetoma may have to be considered if severe haemoptysis occurs.

Actinomycosis

Actinomycosis, which was formerly included amongst the fungal diseases, is now regarded as a bacterial infection. It is caused by *Actinomyces israeli*, a septate anaerobic organism, which exists as a commensal in the human mouth. It presumably gains access to the lungs by aspiration, and may produce a widespread suppurative lobular pneumonia. Empyema, often bilateral, and associated with persistent chest wall sinuses, may develop at a later stage, or occasionally *de novo*. The infection usually responds to benzylpenicillin, given by intramuscular injection in a dose of 2 mega units eight-hourly for six weeks.

Allergic Reactions to Fungi

Fungal allergic reactions may cause bronchial asthma (*A. fumigatus* and *Cladosporium herbarum*), pulmonary eosinophilia (*A. fumigatus*) or allergic alveolitis (*Micropolyspora faeni*, *Thermoactinomyces vulgaris*, *Coniosporium corticale* and *Aspergillus clavatus*). These conditions are described in the following section on allergic diseases of the respiratory tract.

ALLERGIC DISEASES OF THE RESPIRATORY TRACT

Many types of particle suspended in the atmosphere possess antigenic properties, and are capable of stimulating the production of specific antibody when inhaled (p. 30). Further exposure to antigen of an individual 'sensitised' in this way may provoke an allergic reaction which causes pathological changes and disturbances of function in the tissue where the reaction occurs. Three types of allergic response are concerned in the production of respiratory disease. The Type I or anaphylactic response (p. 29), mediated by reaginic antibody (immunoglobulin IgE), is associated with an immediate hypersensitivity reaction, the clinical manifestations of which include allergic rhinitis and bronchial asthma. The Type III or Arthus-type response, mediated by precipitating antibody (immunoglobulin IgG), is associated with a late hypersensitivity reaction which may contribute to the production of allergic alveolitis. Both Type I and Type III responses may be concerned in the production of some forms of pulmonary eosinophilia, such as allergic bronchopulmonary aspergillosis. Type IV or tuberculin-type allergic responses, which are cell mediated and do not involve circulating antibody, are usually associated with delayed hypersensitivity reactions in conditions such as tuberculosis, but may be concerned in predominantly Type III reactions, such as allergic alveolitis.

Ingested antigens, or drugs acting as haptens, such as aspirin and PAS, occasionally produce allergic respiratory disorders, such as bronchial asthma and pulmonary eosinophilia, and auto-antigens may have a similar role in conditions such as polyarteritis nodosa.

In this chapter, allergic rhinitis, bronchial asthma, pulmonary eosinophilia and allergic alveolitis will be described in some detail, but for a description of other forms of allergic disorder the reader should refer to appropriate sections of the book.

Allergic Rhinitis

This is a disorder in which there are episodes of nasal congestion, watery nasal discharge and sneezing. It may be *seasonal* or *perennial.*

Aetiology. Allergic rhinitis is due to a Type I antigen-antibody reaction in the nasal mucosa. The antigens concerned in the seasonal form of the disorder are pollens from grasses, flowers, weeds or trees. Grass pollen is responsible for hay fever, the most common type of seasonal allergic rhinitis in Britain, and this disorder is at its peak between May and July.

Perennial allergic rhinitis may be a specific reaction to antigens derived from house dust, fungal spores or animal dander, but similar symptoms can be caused by physical or chemical irritants, such as pungent odours or fumes, including strong perfumes, cold air and dry atmospheres. In this context the term 'allergic' is a misnomer.

Clinical Features. In the seasonal type there are frequent sudden attacks of sneezing, with profuse watery nasal discharge and nasal obstruction. These attacks last for a few hours, and are often accompanied by smarting and watering of the eyes and conjunctival injection. In the perennial type the symptoms are similar, but more continuous and generally less severe.

Diagnosis. In seasonal allergic rhinitis the diagnosis is usually obvious because the attacks occur only during the pollen season. In the perennial type it may be more difficult, because the symptoms may initially be indistinguishable from those of coryza. In coryza, however, the subsequent appearance of pus in the nasal discharge usually makes the diagnosis clear.

In seasonal allergic rhinitis skin sensitivity tests or nasal provocation tests with the relevant antigen are usually positive, and are thus of diagnostic value, but these tests are less useful in perennial rhinitis, and may be completely unhelpful.

Prognosis. The symptoms of both types of allergic rhinitis, particularly the seasonal type, can usually be controlled by drugs, and in some cases the condition subsides spontaneously. It is to be regarded more as a serious inconvenience than as a disease.

Prevention. In the seasonal type an attempt should be made to avoid exposure to pollen, or at least reduce it to a minimum, for example by avoiding country districts and keeping indoors as much as possible, with the windows closed, during the pollen season.

An antihistamine drug taken daily throughout the pollen season will often prevent attacks of hay fever, but some patients will require pre-seasonal hyposensitisation with a grass pollen extract (Bencard or Dome).

The prevention of perennial rhinitis consists of avoiding, as far as possible, exposure to the various aetiological factors mentioned above. Specific hyposensitisation is of no value.

Treatment. The following symptomatic measures are applicable to both seasonal and perennial allergic rhinitis:

1. Antihistamine drugs, such as chlorpheniramine maleate (Piriton), 4-8 mg thrice daily, often provide considerable or even complete relief of symptoms.

2. Sodium cromoglycate (p. 380), administered by nasal insufflation in a dose of 10 mg into each nostril four times daily (Rynacrom), is a useful preventive measure in about 60 per cent of patients with the seasonal type of allergic rhinitis, but is less effective in the perennial type.

3. Other local measures which may be of value are (*a*) decongestant nasal sprays, using a 1 per cent solution of ephedrine hydrochloride in saline and (*b*) instillations of 1-2 drops of 1 per cent ephedrine in saline into the conjunctival sac.

4. Patients failing to respond to these measures may obtain symptomatic relief from weekly intramuscular injections of 0·5-1 mg of tetracosactrin zinc phosphate complex (Synacthen Depot), but this form of treatment should be reserved for those patients whose symptoms are very severe and interfere seriously with business and social activities.

Bronchial Asthma

Bronchial asthma is characterised by paroxysms of dyspnoea accompanied by wheezing, resulting from temporary narrowing of the bronchi by muscle spasm, mucosal swelling or viscid secretion. The bronchial narrowing interferes with pulmonary ventilation and increases the work of breathing by raising the resistance to air flow within the bronchi. Being more marked during expiration it also causes air to be 'trapped' in the lungs. The narrowed bronchi can no longer be effectively cleared of mucus by the act of coughing, and obstruction of many of the smaller bronchi by inspissated and often very tenacious secretion adds to the respiratory embarrassment. In fatal cases this is usually the most conspicuous finding at autopsy.

Aetiology. Asthma may begin at any age, but in most cases it starts either in childhood or in middle age. 'Early onset' asthma is slightly more common in males, and 'late onset' asthma in females. 'Early onset' asthma occurs in atopic individuals, i.e. those who readily form reaginic antibodies to commonly encountered allergens (p. 30). Such individuals can be identified by skin sensitivity tests (p. 378), which give positive reactions with a wide range of common allergens. They often suffer from other allergic disorders, such as allergic rhinitis and eczema, and a family history of these disorders and of 'early onset' asthma is common. It is unusual for a single allergen to be the sole cause of asthma, and clinical experience indicates that many different allergens are implicated in almost every case, although the importance of each of them may vary from time to time. 'Late onset' asthma generally occurs in non-atopic individuals, and it would appear that external allergens play no part in the production of this form of the disease, to which the term 'intrinsic asthma' is sometimes applied.

The allergens responsible for asthma in atopic individuals generally enter the bronchi with the inspired air, and are derived from organic material, such as pollen, mite-containing house dust, feathers, animal dander and fungal spores. Previous exposure to these agents will have stimulated the formation of reaginic antibody (the immunoglobulin IgE), and a Type I antigen-antibody reaction in the bronchi may follow further exposure to specific allergen. This releases pharmacologically active substances, such as histamine, bradykinin, slow-reacting substance (SRS-A) and serotonin, which promote bronchial constriction and an inflammatory reaction of allergic type in the bronchial mucosa. Much less frequently, similar effects may be produced by ingested allergens derived from certain foods, such as fish, eggs, milk, yeasts and wheat, which presumably reach the bronchi via the blood stream. Ingested non-protein substances, particularly drugs, of which aspirin is a notable example, occasionally cause asthma by forming haptens.

It is possible that a Type III allergic reaction may also be implicated in the pathogenesis of bronchial asthma, particularly where antigens derived from fungi, such as *A. fumigatus*, are concerned, but for more information on this matter the reader should refer to a textbook of immunology.

Regardless of whether asthma occurs in atopic or non-atopic individuals, the symptoms are often aggravated by non-specific factors, such as bronchial irritation caused by tobacco smoke, dust, acrid fumes and cold air, bacterial infection in the respiratory tract, and emotional stress. Strenuous exertion can also provoke an asthmatic attack in predisposed individuals, particularly children.

Clinical Features. Bronchial asthma may be either *episodic* or *chronic*, and although there is a good deal of overlap between these two syndromes, the distinction is clinically useful, particularly in terms of prognosis and management. In general, atopic individuals tend to develop episodic asthma, and non-atopic individuals chronic asthma.

In typical cases of episodic asthma the paroxysms, which may occur at any hour of the day or night, are of sudden onset, but may be preceded by a feeling of tightness in the chest. The dyspnoea, which may be intense, is chiefly expiratory in character. Expiration becomes a conscious and exhausting effort, in contrast to inspiration which is short and gasping. The patient adopts an upright position, fixing the shoulder-girdle to assist the accessory muscles of expiration. Wheezing, chiefly expiratory, is heard, and there may be an unproductive cough which aggravates the dyspnoea. In severe attacks the pulse is rapid, and central cyanosis may be present.

The attack may end abruptly within an hour or two, sometimes with the coughing up of tough viscid sputum, but a less intense degree of expiratory wheeze may persist for many hours or even for several days before subsiding gradually. The term *status asthmaticus* describes a state of intense asthma which persists for many hours or days. The sputum, usually scanty, may contain numerous eosinophil leucocytes and, occasionally, gelatinous casts of small bronchi. In most cases there is an increase in the number of eosinophil leucocytes in the blood to 500-1,500 per mm^3.

In *chronic asthma* the paroxysmal character of the symptoms is usually less conspicuous, the chief clinical features being continuous wheeze and breathlessness on exertion. Cough and mucoid sputum, with recurrent episodes of frank respiratory infection, are common in this type of asthma, and may be due to associated chronic bronchitis.

PHYSICAL SIGNS IN THE CHEST. 1. During a paroxysm the chest is held near the position of full inspiration. The percussion note may be hyper-resonant. The breath sounds, which are obscured by numerous high-pitched musical rhonchi, are vesicular in character with prolonged expiration. In very severe asthma airflow may be insufficient to produce rhonchi, and a 'silent chest' in such patients is an ominous sign.

2. Between paroxysms there are usually no abnormal physical signs except in patients with chronic asthma, who are seldom without rhonchi. Severe asthma starting in childhood usually causes a 'pigeon chest' deformity.

RADIOLOGICAL EXAMINATION. In uncomplicated bronchial asthma the chest radiograph is normal. In long-standing cases the signs of emphysema (p. 391) may be present, and the lateral view may demonstrate a 'pigeon chest' deformity. Occasionally, when a bronchus is obstructed by tenacious mucus, there is an opacity caused by lobar or segmental collapse.

PULMONARY FUNCTION TESTS. Measurements of the forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) or of the peak expiratory flow rate (PEFR) provide a fairly reliable indication of the degree of airway obstruction (p. 328), and can also be used to determine whether and to what extent it can be relieved by bronchodilator drugs or corticosteroids. Such tests thus have an important place in the diagnosis and treatment of bronchial asthma. Measurements of arterial blood gas pressures (Pa_{O_2} and Pa_{CO_2}) are indispensable to the management of patients with status asthmaticus (p. 379).

SKIN SENSITIVITY TESTS. A tiny prick is made in the skin through a drop of a specially prepared solution of the substance to be tested, and a positive reaction is indicated by the development of a wheal, which begins to appear within a few minutes. Tests are usually performed with solutions of all the common substances known to possess antigenic properties. It is seldom possible with these tests to identify one particular substance as the cause of asthma in an individual case, and their chief value is to distinguish atopic from non-atopic subjects.

Diagnosis. Bronchial asthma seldom presents problems in diagnosis, except at the beginning, when it may be difficult to distinguish from left ventricular failure (p. 244) and tracheal obstruction (p. 386). Chronic asthma and chronic bronchitis often coexist, but a good response to bronchodilator drugs or corticosteroids suggests that asthma is the predominant condition.

Course and Prognosis. The prognosis of the individual attack is good, except in severe status asthmaticus where there is occasionally a fatal outcome. Spontaneous recovery is fairly common in episodic asthma, particularly in children, but rare in chronic asthma, which often causes severe pulmonary damage. Seasonal fluctuations occur in both types of asthma. Atopic subjects with episodic asthma are usually worse in the summer, when they are more heavily exposed to antigens, while chronic asthmatics are usually worse in the winter months because of their increased liability to bacterial infection.

Treatment

1. MANAGEMENT OF AN ASTHMATIC ATTACK. The patient should be allowed to take up the position which he finds most comfortable, either propped up in bed or sitting in a chair. If central cyanosis is present, oxygen should be administered with an M.C. mask (p. 331). Ephedrine, 30-60 mg by mouth, may be sufficient to abort a mild attack, but β-adrenergic receptor stimulant drugs, such as salbutamol (4 mg) and terbutaline (5 mg), are more effective bronchodilators. These two drugs are also less liable to produce palpitation and tachycardia, and are gradually replacing ephedrine for the oral treatment of asthmatic attacks. The same two drugs can, perhaps even more effectively, be given by inhalation from pressurised dispensers. A Ventolin inhaler provides a metered dose of 100 micrograms of salbutamol, and a Bricanyl inhaler 250 micrograms of terbutaline. For maximum bronchodilatation two doses ('puffs') should be inhaled at a time, the second five minutes after the first. The relief obtained usually lasts for three to four hours. It is seldom profitable, and possibly unsafe, to repeat the inhalation within this period. Isoprenaline, which is also available for inhalation from a pressurised dispenser, has a more pronounced action on cardiac β-receptors than the other two drugs, and is potentially more dangerous in the presence of hypoxia. It should therefore not be used in the treatment of asthma.

Adrenaline injection (B.P.), 0·5 mg subcutaneously, occasionally relieves an attack which has failed to respond to inhalations of salbutamol or terbutaline, but it may be no less dangerous than isoprenaline in hypoxic subjects, and in these circumstances aminophylline, 0·25-0·5 g in 10-20 ml of sterile water, injected slowly intravenously may be safer and is often more effective.

Status asthmaticus is usually relieved by the administration of one of the corticosteroid group of drugs, and in some instances this may be the only means of averting a fatal outcome. In a case of average severity prednisolone should be given by mouth in a dose of 15 mg six-hourly on the first day, 10 mg six-hourly on the second, and 5 mg six-hourly thereafter. Patients who are gravely ill should receive 100 mg of prednisolone by mouth in the first 12 hours, along with hydrocortisone hemisuccinate intravenously in a dose of 100-200 mg four-hourly. It may be some hours before such patients begin to respond to corticosteroids, but during this critical period the airway obstruction can often be relieved by a 0·5 per cent salbutamol aerosol in 40 per cent oxygen administered by intermittent positive-pressure ventilation (using a Bennett or Bird ventilator and a tightly fitting face mask) for three minutes every one to two hours. Hypoxia is always present and must be treated with the highest possible concentration of oxygen consistent with the maintenance of a normal or subnormal $Paco_2$. If facilities for arterial blood gas studies are not available a 35 per cent Ventimask (p. 331) should be used. Metabolic acidosis and dehydration, which increases the viscosity of the sputum, must be corrected. If the patient's condition continues to deteriorate, and particularly if the $Paco_2$ rises above 50 mm Hg, intermittent positive-pressure ventilation via a cuffed oro-tracheal tube (p. 332) should be instituted.

Unless the patient is being artificially ventilated, hypnotics should be used with caution and opiates must never be given. Diazepam, 5-10 mg intramuscularly, is relatively safe, and may promote relaxation and sleep. As status asthmaticus is often complicated by respiratory infection, which may not always be readily recognisable in the early stages, a suitable antibiotic (p. 329) should be administered in every case.

The usual procedure after the patient begins to recover is to continue treatment with prednisolone in diminishing dosage for 10 to 14 days. Corticosteroids have, however, only a temporary suppressive effect, and asthma frequently recurs a few weeks or even a few days after treatment is stopped.

2. TREATMENT OF CHRONIC ASTHMA. Patients who have frequent recurrences of episodic bronchial asthma and those with chronic asthma present a special problem in management, as many of them are incapacitated for prolonged periods by breathlessness on exertion. In some cases the symptoms can be kept in check by bronchodilator drugs given by mouth or by inhalation as often as necessary. For oral treatment it is customary to prescribe drugs such as salbutamol (4 mg), terbutaline (5 mg), ephedrine (30 mg) or choline theophyllinate (200 mg) four times daily, but frequent inhalations of salbutamol or terbutaline are probably more effective. Severe chronic asthma responds only transiently to these measures, and many such patients require regular treatment with corticosteroids by mouth or by inhalation. Before this is started, however, it is important to confirm, by serial recordings of FEV, that a short (7-day) course

of prednisolone by mouth produces significant improvement. If a satisfactory response is recorded, and the symptoms are not particularly severe, asthma can often be adequately controlled by a topical corticosteroid preparation, beclomethasone (Becotide), administered by inhalation from a pressurised dispenser in two metered doses of 50 μg four times daily. Since very little of this small dose of corticosteroid will be absorbed from the bronchial mucosa, systemic side-effects seldom occur but faucial candidosis (thrush) may be a troublesome local complication. If this form of treatment is not effective, it will have to be supplemented by oral prednisolone in a dose of up to 10 mg per day. In such cases the risk of serious side-effects must be weighed against the dangers of uncontrolled asthma and the degree of disability for which it is responsible.

3. MANAGEMENT OF FACTORS OF AETIOLOGICAL IMPORTANCE

(*a*) *Allergy*. The patient should try to avoid allergens which may be contributing to the production of his asthma. This may not be difficult when the allergy is to substances such as animal dander, feathers, articles of diet or drugs, but it is virtually impossible in the case of ubiquitous allergens such as pollens or fungal spores. Efforts can, however, be made to reduce the amount of dust in bedrooms occupied by patients who are sensitive to allergens present in house dust. Vacuum cleaning of mattresses is particularly useful, as dust from this source contains large numbers of mites, which contribute significantly to the antigenicity of house dust.

Hyposensitisation (p. 375) with extracts of antigenic substances is of little or no value, except in the case of grass pollen allergy, which can sometimes be controlled in this way. Suitable preparations for mixed grass pollen hyposensitisation are Alavac P (Bencard) and Allpyral G (Dome).

Antihistamine drugs are of no value in the prevention of bronchial asthma, but sodium cromoglycate (Intal) (p. 39), which is believed to act by preventing the release of bronchoconstrictor substances from mast cells in the bronchial wall, has a useful prophylactic effect in about 40 per cent of asthmatics. The best results are obtained in atopic subjects. A dose of 20 mg four times daily by inhalation should be given initially, but a smaller maintenance dose is adequate in many cases.

(*b*) *Respiratory Infection*. Where the attacks of asthma are clearly related to bacterial infection they can often be prevented if the infection is controlled promptly by an antibiotic (p. 329).

(*c*) *Exertion*. Exercise-induced asthma (p. 376) can often be prevented by the inhalation of a bronchodilator aerosol a few minutes previously, or by regular treatment with sodium cromoglycate.

(*d*) *Emotional Disturbance*. Sedation is indicated if emotional stress appears to be present. For this purpose diazepam in a dose of 5-10 mg thrice daily is usually adequate. An attempt should be made to deal with causes of friction and anxiety. This can usually best be done by the family doctor, but the assistance of a psychiatrist may be required in some cases.

4. BREATHING AND POSTURAL EXERCISES. The main purpose of these exercises is to prevent chest deformity and defective posture, which are prone to develop in all patients with asthma, especially children.

Pulmonary Eosinophilia

This term is applied to a rather heterogeneous group of conditions which have two features in common—an increase in the number of circulating eosinophil leucocytes and transient radiographic opacities in the lungs. These conditions can be classified as follows:

1. Simple pulmonary eosinophilia (Löffler's syndrome).
2. Tropical pulmonary eosinophilia.
3. Asthmatic pulmonary eosinophilia (including allergic broncho-pulmonary aspergillosis).
4. Polyarteritis nodosa.

Simple Pulmonary Eosinophilia. This is probably a Type I or Type III immune reaction in the lung to various foreign proteins and to certain drugs presumably acting as haptens. In tropical countries the antigen is usually derived from helminth larvae, including ascaris and schistosomes, as they migrate through the lungs, but in temperate regions the antigenic agent is usually a drug, such as PAS, nitrofurantoin or a sulphonamide. A mild degree of pyrexia and a slight cough are often the only clinical abnormalities, radiographic examination shows transient pulmonary opacities, and the eosinophil count in the blood is slightly or moderately increased (500-1,500 per mm^3). Treatment consists of eradicating the parasitic infestation or withdrawing the offending drug.

Tropical Pulmonary Eosinophilia. This condition occurs mainly in India and Ceylon, and is thought to be an allergic reaction to microfilariae in the lung. There is a persistent cough with or without asthma, pyrexia, miliary shadowing on the chest radiograph and a marked degree of eosinophilia in the blood (more than 2,000 per mm^3). The illness usually responds to treatment with diethylcarbamazine (p. 977).

Asthmatic Pulmonary Eosinophilia. This condition is due in most cases (estimates vary between 50 and 90 per cent) to combined Type I and Type III immune reactions (p. 28) in the bronchi and lungs to the fungus *Aspergillus fumigatus*. The allergens responsible for the other cases have not yet been identified. The condition is invariably associated with chronic asthma, and the eosinophil count in the blood is usually between 500 and 1,500 per mm^3. The pulmonary lesions are of two types: (1) segmental or subsegmental (occasionally lobar) collapse caused by occlusion of the related bronchus by a mucinous cast coated with eosinophils, which often contains fungal hyphae, and (2) areas of pulmonary infiltration in which the alveolar spaces and alveolar walls contain numerous eosinophils, and varying numbers of lymphocytes and plasma cells. The first type of lesion is more common than the second. The radiographic appearances reflect the pathological changes—absorption collapse of a segment, or of a larger or smaller bronchopulmonary unit, in the first type, and an ill-defined pulmonary opacity in the second. These lesions may recur at intervals for many years, anywhere in the lungs, but more often involving the upper lobes. Bronchiectasis frequently develops in collapsed bronchopulmonary segments.

When allergic bronchopulmonary aspergillosis is responsible for the pulmonary eosinophilia, the diagnosis can usually be made by mycological examination of the sputum or of a bronchial cast, combined with skin sensitivity tests and serological tests. In most cases *A. fumigatus* can readily be isolated on culture. An extract prepared from this fungus gives a positive skin reaction (in which there may be 'immediate' and 'late' components), and a positive gel diffusion test (which indicates the presence of precipitating antibody).

Treatment of this condition can be very difficult. Efforts to eliminate the fungus from the respiratory tract by regular inhalations of natamycin seldom succeed. Antihistamines are of no value, but corticosteroids may relieve the asthma, and at the same time prevent recurrent pulmonary infiltrations and the formation of new bronchial casts. If established casts cannot be dislodged by postural drainage they should be extracted through a bronchoscope. Failure to deal effectively with these casts is an important factor in the production of bronchiectasis.

Polyarteritis. This disease may present with respiratory symptoms, including asthma, recurrent pulmonary opacities on radiological examination, and a moderate increase in the eosinophil count. Other organs are usually involved at a later stage. The condition is described on page 305.

Allergic Alveolitis

In this condition the inhalation of certain types of organic dust produces a diffuse allergic reaction in the walls of the alveoli and bronchioles. There is a cellular exudate consisting of polymorphs, lymphocytes and plasma cells, and small epithelioid granulomata may also be seen. These changes cause decreased pulmonary compliance and ventilation: perfusion inequalities. They are presumably also responsible for the widespread coarse crepitations heard on auscultation, and for the diffuse micronodular shadowing seen on the chest radiograph. Precipitating antibodies in the serum against the relevant antigens would seem to indicate that allergic alveolitis is a Type III immune reaction, but the finding of small pulmonary granulomata suggests that a Type IV immune reaction may also be implicated (p. 35).

Some of the agents which produce allergic alveolitis, the source of these agents, and the names applied to the resulting diseases are shown in Table 6 (p. 383). The term *extrinsic* allergic alveolitis is sometimes applied to this group of diseases, to indicate that the antigen is of external origin. If patients with this disorder continue to expose themselves to the relevant antigen for long periods, they may eventually develop permanent pulmonary damage with severe respiratory disability.

Allergic alveolitis should be suspected when a person regularly exposed to a heavy concentration of organic dust complains, a few hours after re-exposure to the same dust, of general malaise, dry cough and dyspnoea without wheeze. If the cause of these symptoms is not appreciated, and further exposure to the dust hazard permitted, they are likely to become continuous, and in some cases very severe. At this stage the patient may be febrile, cyanosed and dyspnoeic at rest, coarse crepitations (but no rhonchi) can be heard all over the chest and a chest radiograph will show diffuse micronodular shadowing. The FEV_1 and FVC are both reduced, but the FEV_1/FVC ratio is normal—indicating a restrictive ventilatory defect without airway obstruction. The Pa_{O_2} is reduced, and the Pa_{CO_2} is slightly subnormal as a result of overventilation.

TABLE 6

Types and Causes of Extrinsic Allergic Alveolitis

Agent	Source	Disease
Micropolyspora faeni	Mouldy hay	Farmer's lung
Thermophilic actinomycetes	Compost	Mushroom worker's lung
	Mouldy sugar cane fibre	Bagassosis
Aspergillus clavatus	Malting barley	Maltworker's lung
Coniosporium corticale	Bark of maple trees	Maple bark disease
Avian protein in pigeon and budgerigar droppings	Pigeon loft or bird cage	Bird fancier's lung
Proteolytic enzyme derived from *Bacillus subtilis*	Air-borne dust in factory making 'biological' washing powder	Terminology undecided

The diagnosis of allergic alveolitis is confirmed serologically by a positive precipitin test and, if necessary, by a positive provocation test, in which the inhalation of an aerosol containing the relevant antigen is followed after three to six hours by pyrexia and a reduction in FVC, often associated with a recurrence of symptoms.

Mild forms of allergic alveolitis rapidly subside when exposure to the dust ceases. In severe cases a corticosteroid preparation should be given for three to four weeks, starting with 40-60 mg of prednisolone per day. Severely hypoxic patients may require oxygen in high concentration (60 per cent).

DISEASES OF THE LARYNX

Acute infections of the larynx have already been described (p. 339). Other common disorders of the larynx include chronic laryngitis, laryngeal tuberculosis (p. 358), laryngeal paralysis and laryngeal obstruction. Tumours of the larynx are relatively common, but for information on these conditions the reader should refer to a textbook of diseases of the ear, nose and throat.

Chronic Laryngitis

Aetiology. Chronic laryngitis occurs as a result of:

1. Repeated attacks of acute laryngitis.
2. Excessive use of the voice, especially in dusty atmospheres, e.g. in auctioneers.

3. Heavy tobacco smoking.
4. Mouth breathing from nasal obstruction.
5. Chronic nasal and oral sepsis.

Pathology. The surface of the mucous membrane is dry and covered with small papillary projections. The vocal cords are thickened and opaque. Microscopically the submucosa is infiltrated with chronic inflammatory cells.

Clinical Features. The chief symptom is hoarseness and the voice may be lost. There is irritation of the throat and spasmodic cough with a little mucoid sputum.

Diagnosis. As chronic and progressive hoarseness may also be caused by tuberculosis and tumours of the larynx and by laryngeal paralysis, these conditions must be considered in the differential diagnosis if the hoarseness does not improve within a few weeks. In some cases a chest radiograph may bring to light unsuspected pulmonary tuberculosis or a bronchial carcinoma. If no such abnormality is found the patient should be referred to a specialist for laryngoscopic examination.

Treatment. The voice must be rested completely. This is particularly important in the case of public speakers. Smoking should be prohibited. Some benefit may be obtained from frequent inhalations of steam medicated with benzoin or menthol. Predisposing conditions such as nasal and oral sepsis must be remedied.

Course and Prognosis. The disease pursues a chronic course frequently uninfluenced by treatment, and in long-standing cases the voice is often permanently impaired.

Laryngeal Paralysis

Aetiology. Laryngeal paralysis may be organic or functional.

Organic paralysis is due to interference with the motor nerve supply of the larynx and may be caused by:

1. Lesions of the brain stem, e.g. bulbar paralysis due to vascular lesions, motor neurone disease or poliomyelitis.
2. Toxic and infective lesions of the vagus nerve or its recurrent laryngeal branch, e.g. polyneuritis, diphtheritic or lead neuropathy.
3. Interruption of the recurrent laryngeal nerve, or of the vagus trunk above the origin of that nerve, by tumour, aneurysm or trauma (p. 824). This is the most common way in which laryngeal paralysis is produced. The paralysis is nearly always unilateral and, by reason of the intrathoracic course of the left recurrent laryngeal nerve, usually left-sided. Accidental division of one or both recurrent laryngeal nerves is one of the hazards of thyroidectomy.

Functional paralysis of the larynx occurs as a manifestation of hysteria.

Clinical Features

1. *Hoarseness* always accompanies laryngeal paralysis whatever its cause. Paralysis of organic origin is seldom reversible, but when only one vocal cord is affected the hoarseness may improve or even disappear after a few weeks as a result of a compensatory adjustment whereby the unparalysed cord crosses the mid-line and approximates with the paralysed cord on phonation.
2. '*Bovine*' *cough*, which is a characteristic feature of organic laryngeal paralysis, results from the loss of the explosive phase of normal coughing consequent upon the failure of the cords to close the glottis. The difficulty in bringing up sputum which some of these patients experience can be explained on the same basis. 'Bovine' cough does not occur with hysterical paralysis.
3. *Dyspnoea* and *stridor* are occasionally present but are seldom severe except with bilateral laryngeal paralysis of organic origin.
4. *Laryngoscopy* is necessary to establish the diagnosis of laryngeal paralysis with certainty. The paralysed cord lies in the so-called 'cadaveric' position, midway between abduction and adduction. In hysterical paralysis only adduction of the cords, a voluntary movement, is affected.

Treatment. The treatment is that of the underlying disease. The psychological basis for hysteria should be determined and, if possible, adjusted. In bilateral paralysis of organic origin the passage of an endotracheal tube or even tracheostomy may be required for the relief of laryngeal obstruction (below). Eventually, in these cases, it may be necessary to perform a plastic operation on the larynx in order to secure permanent restoration of the airway.

Laryngeal Obstruction

Aetiology. The laryngeal opening (glottis) may be obstructed by (1) inflammatory or allergic oedema or exudate, (2) spasm of the laryngeal muscles, (3) inhaled foreign body, (4) inhaled vomitus in an unconscious patient, (5) tumours of the larynx, (6) bilateral vocal cord paralysis and (7) fixation of both cords in advanced rheumatoid arthritis. Laryngeal obstruction is more liable to occur in children than in adults because of the smaller size of the glottis.

Clinical Features. These depend on whether the obstruction is complete or incomplete and on the rapidity of its onset.

Sudden complete laryngeal obstruction by a foreign body produces the clinical picture of acute asphyxia—violent but ineffective inspiratory efforts with indrawing of the intercostal spaces and the unsupported lower ribs, accompanied by deep cyanosis. Unrelieved, the condition progresses rapidly to coma, and death ensues within 5 to 10 minutes. When, as in most cases, the obstruction is incomplete at first, the main clinical features are progressive dyspnoea and cyanosis, stridor and indrawing of the intercostal spaces and lower ribs on both sides. The great danger in these cases is that the obstruction may at any time become complete and result in sudden death.

Treatment. Transient attacks of laryngeal obstruction due to exudate and spasm, which may occur with acute laryngitis in children (p. 336) and with whooping-cough, are potentially dangerous but can usually be relieved by the inhalation of steam.

Laryngeal obstruction from all other causes carries a high mortality and demands prompt treatment. The following measures may have to be employed:

1. *The relief of obstruction by mechanical means.* When a foreign body is known to be the cause of the obstruction it can often be dislodged by turning the patient head downwards and thumping his back vigorously. In other circumstances the nature of the obstruction should be ascertained whenever possible by direct laryngoscopy, which may also permit the removal of a foreign body or the insertion of a tube past the obstruction into the trachea.

Tracheostomy must be performed without delay if these procedures to relieve the obstruction fail, but except in dire emergencies the operation should be performed in the operating theatre by a surgeon.

2. *Treatment of the cause.* In cases of diphtheria, antitoxin should be administered and for other infections the appropriate antibiotic should be given. In angioneurotic oedema the patient should receive adrenaline, 0·5-1·0 ml of 1:1000 solution subcutaneously, and hydrocortisone hemisuccinate, 100 mg intravenously. It must be remembered that these remedies take time to act and that tracheostomy may be required in the intervening period.

DISORDERS OF THE TRACHEA

Acute tracheitis is a common complication of viral and bacterial infection of the upper respiratory tract, and is usually associated with acute bronchitis (p. 339). Other primary disorders of the trachea are rare. Intrinsic benign and malignant tumours may produce tracheal obstruction, but external compression by enlarged mediastinal lymph nodes containing metastatic deposits from a bronchial carcinoma is a much more common cause of tracheal obstruction. Rarely, the trachea may be compressed by an aneurysm of the aortic arch, or in children by tuberculous mediastinal lymph nodes (p. 397). Tracheal stricture is an occasional complication of tracheostomy.

Stridor (p. 322) can be detected in every patient with major tracheal obstruction. Endoscopic examination of the trachea should be undertaken without delay in these patients to determine the degree of tracheal obstruction and its nature. Localised tumours of the trachea can be resected, but reconstruction of the resected segment may present complex technical problems. The application of deep X-rays or the administration of cytotoxic drugs may temporarily relieve tracheal compression by malignant lymph nodes. Tracheal strictures can sometimes be dilated, but may have to be resected.

A tracheo-oesophageal fistula may be present in new-born infants as a congenital abnormality. In adults, this is usually due to malignant lesions in the mediastinum, such as carcinoma or reticulosis, eroding both the trachea and oesophagus, to produce a communication between them. Swallowed liquids enter the trachea and bronchi through the fistula, and provoke a 'spluttering' cough. Surgical closure of a congenital fistula, if undertaken promptly, is usually successful, but malignant fistulae are incurable, and death from overwhelming pulmonary infection rapidly supervenes.

CHRONIC BRONCHITIS AND EMPHYSEMA

Chronic Obstructive Airway Disease

Although chronic bronchitis and emphysema are pathologically distinct, they frequently co-exist, and it may then be difficult or impossible to determine the relative importance of each condition in the individual case. Generalised airway obstruction is a prominent feature of both diseases. In chronic bronchitis it is chiefly due to swelling of the bronchial mucosa and the accumulation of tenacious mucus within the air passages. In emphysema, on the other hand, the main factor in the production of airway obstruction is extramural bronchial compression and collapse caused by overdistended alveoli in which air has been 'trapped' during expiration. This phenomenon is aggravated by chronic bronchitis and bronchopulmonary infection.

Chronic bronchitis and emphysema are often grouped together under the heading of 'chronic obstructive airway disease', and can be regarded as forming a spectrum, with 'pure' chronic bronchitis at one end and 'pure' emphysema at the other. For descriptive purposes, however, it is convenient to deal with them separately, with emphasis on their similarities and differences, and on the relationships which frequently exist between them.

Chronic Bronchitis

Aetiology. Chronic bronchitis is the name given to the clinical syndrome which many individuals develop in response to the long-continued action of various types of irritant on the bronchial mucosa. The most important of these is tobacco smoke, but they also include dust, smoke and fumes, occurring as specific occupational hazards or as part of a general atmospheric pollution in industrial cities and towns. Infection is sometimes a precipitating factor in the onset of chronic bronchitis, but its main role is in aggravating the established condition. Exposure to dampness, to sudden changes in temperature and to fog may also be responsible for exacerbations of chronic bronchitis.

The disorder occurs most commonly in middle and late adult life. More males are affected than females and there may be a familial predisposition. As might be expected, it is more common in smokers than in non-smokers, and in urban than in rural dwellers.

Culture of the sputum may yield merely a mixture of naso-pharyngeal commensals, but pathogens such as *Strept. pneumoniae* and *H. influenzae* are often isolated. These organisms become more numerous during acute exacerbations of infection.

Pathology. In all cases there is overactivity of the mucus-secreting glands and goblet cells in the bronchi and bronchioles. The vast excess of mucus so produced coats the bronchial walls and clogs the bronchioles. Mucosal oedema further reduces the calibre of the air passages and as the degree of obstruction is greater during expiration air is 'trapped' in the alveoli. With the passage of time the alveoli become permanently over-distended and there is extensive rupture of their walls. Sooner or later, infection supervenes and this leads to widespread destruction of the bronchioles and pulmonary lobules by what is in effect a low-grade suppurative bronchopneumonia. Compensatory over-distension of the surviving alveoli adds to the disorganisation of pulmonary structure. These changes, which contribute to the syndrome of 'emphysema', are more fully discussed on page 390.

Clinical Features. The disease usually starts with repeated attacks of 'winter cough', which show a steady increase in severity and duration with successive years, until cough is present all the year round. Wheezing and tightness in the chest are common complaints, especially in the morning before the bronchial secretions are cleared, often with difficulty, by coughing. The sputum may be scanty, tenacious, mucoid, and occasionally streaked with blood, or copious and watery. A frankly purulent sputum is indicative of bacterial infection, which supervenes from time to time in most cases of chronic bronchitis.

Dyspnoea in chronic bronchitis is in most cases a direct consequence of the destruction and disorganisation of pulmonary tissue. It may, however, be aggravated by airway obstruction, caused by infection or by an increase in mucosal oedema which may be produced by cigarette smoking and by adverse atmospheric conditions.

Variable numbers of inspiratory and expiratory rhonchi, mainly low and medium pitched, are present in most cases of chronic bronchitis and there may also be some coarse crepitations. Physical signs attributable to emphysema (p. 391) co-exist in some cases.

Radiological Examination. Chronic bronchitis produces no characteristic abnormality in the radiograph, but bronchography shows various irregularities of bronchial calibre, outline and branching. The features of emphysema (p. 391) may be prominent in advanced cases.

Pulmonary Function Tests

1. In all cases the forced expiratory volume in one second (FEV_1) is reduced, and the ratio of FEV_1 to forced vital capacity (FVC) is also subnormal. In a patient with advanced emphysema the FEV_1 may be less than 1 *l*, and the FEV_1/FVC ratio may be as low as 30 per cent. Such changes are common to all forms of obstructive airway disease (p. 328).

2. Because of 'air trapping' and alveolar distension the residual volume of the lungs is increased at the expense of vital capacity.

3. As the distribution of ventilation and perfusion within the lungs becomes disturbed (p. 319), the Pa_{O_2} falls below normal.

4. In the later stages, when generalised alveolar underventilation (p. 318) supervenes, often following an infective exacerbation of chronic bronchitis, there is a further fall in Pa_{O_2} and a rise in Pa_{CO_2} accompanied by respiratory acidosis (p. 204).

Diagnosis. It is necessary to exclude other conditions, which may be associated with chronic cough, such as:

1. Chronic pulmonary tuberculosis, by repeated examination of the sputum for acid-fast bacilli and by radiological examination.
2. Bronchiectasis (p. 393).
3. Bronchial carcinoma (p. 401).

Course and Prognosis. Chronic bronchitis is usually a progressive disease, punctuated by acute exacerbations and remissions, and eventually causing ventilatory and cardiac failure (p. 246). Some patients die within five years of the onset of symptoms, while others survive for 20 to 30 years, with a steadily diminishing respiratory reserve. In some cases, however, chronic bronchitis is a relatively benign condition which remains static for many years.

Prophylaxis. The control of atmospheric pollution in urban areas and the increased use of measures to prevent the inhalation of dust by industrial workers would undoubtedly reduce the prevalence of chronic bronchitis. In individual cases the abandonment of tobacco smoking and the prompt treatment of acute respiratory infections are important preventive measures.

Treatment

1. *Bronchial irritation* must be reduced to a minimum. If a tobacco smoker, the patient should be urged to give up the habit completely and permanently. Dusty and smoke-laden atmospheres should be avoided. This may require a change of occupation or environment, often involving a reduction of income. Most patients find it difficult to accept this advice, but in a condition as potentially serious as chronic bronchitis it is important to point out that if exposure to dust or smoke continues the patient may become totally incapacitated long before he reaches retiring age.

2. *Respiratory infection* must be promptly controlled, as every such episode may cause further permanent damage to the lungs. The patient should be instructed to observe the colour of his sputum every morning, and if it becomes purulent he should be given tetracycline or ampicillin in a dose of 250 mg four times daily or co-trimoxazole, 2 tablets twice daily, for five to seven days. Intelligent patients can be provided with a stock of antibiotic tablets, and permitted to start a course of treatment on their own initiative when the need arises.

As the vast majority of bacterial infections in chronic bronchitis are caused by *Strept. pneumoniae* or *H. influenzae*, bacteriological examination of sputum is essential only when the response to standard treatment is unsatisfactory, and the sputum remains purulent. In that event a change of antibiotic, guided by the results of bacterial sensitivity tests, will be indicated. If *Staph. pyogenes* is isolated, antibiotics such as cloxacillin or sodium fusidate (p. 161) will be required.

Continuous suppressive treatment with tetracycline or ampicillin, given throughout the winter or even throughout the year, is not advised, since it is apt to promote the emergence of a drug-resistant respiratory tract flora, and may merely add to the therapeutic problems.

3. *Symptomatic measures* may be required to control unproductive cough during the night, to enable sputum to be coughed up more easily and to relieve breathlessness and wheeze. Nocturnal unproductive cough will often be less troublesome if the patient sleeps in a heated bedroom, but pholcodine or methadone (p. 333) may be required to control it. A hot drink or the inhalation of steam helps to liquefy sputum and make it easier to bring up. So-called expectorant cough mixtures are of little or no value. Measures for the relief of asthmatic symptoms are described on page 378.

4. *Ventilatory failure* must be promptly treated (p. 332).

Emphysema

The word 'emphysema' means 'inflation' in the sense of unnatural distension with air, and this phenomenon, thus defined, can occur anywhere in the body. Air may, for example, enter the mediastinum (*mediastinal emphysema*) following the rupture of overdistended alveoli into the interstitial tissues of the lung in patients with severe bronchial asthma, or following rupture of the oesophagus. If a very large amount of air escapes rapidly into the mediastinum, it may produce cardiac tamponade (p. 288), but in most cases it tracks harmlessly upwards into the soft tissues of the neck, where it imparts a characteristic crackling sensation to the palpating fingers (*subcutaneous emphysema*). Penetrating wounds of the chest wall may also cause subcutaneous emphysema, and when a spontaneous pneumothorax is treated by pleural decompression with an intercostal tube (p. 424), widespread subcutaneous emphysema is an occasional complication, which is alarming but not serious.

Pulmonary Emphysema

The term 'pulmonary emphysema' covers a wide variety of pathological processes, ranging from overdistension of otherwise normal alveoli in conditions such as bronchial asthma (p. 375), obstructive emphysema (p. 396) and compensatory emphysema (p. 397) to the widespread disruption of the alveolar walls which occurs in the more serious forms of pulmonary emphysema. There is a close association between the latter and chronic bronchitis, but the physical signs and radiological changes attributable to 'emphysema' may be more conspicuous in some cases of chronic bronchitis than in others. Chronic bronchitis and emphysema can both cause severe pulmonary damage, but it is of a different type in the two conditions. In chronic bronchitis it is mainly due to progressive destruction of bronchopulmonary lobules by bacterial infection, whereas in emphysema generalised destruction of the alveolar walls ('panacinar' emphysema) is the dominant lesion. Where emphysema occurs along with a major component of chronic bronchitis, it is usually 'centrilobular' or 'centriacinar', and principally affects those alveoli which are most closely related to the respiratory bronchioles. Although these two types of emphysema develop in different ways, factors such as bacterial infection and alveolar overdistension caused by distortion of the airways may eventually blur their distinctive features.

The predominance of either chronic bronchitis or emphysema may, however, be sufficiently clear-cut to produce two separately identifiable syndromes (Table 7). In the chronic bronchitis syndrome, ventilatory function is fairly well preserved, but severe hypoxia and hypercapnia, pulmonary hypertension and right ventricular failure occur at an early stage. In the emphysema syndrome, on the other hand, grave impairment of ventilatory function and disabling exertional dyspnoea may antedate by many years the manifestations of respiratory and cardiac failure. A mixed syndrome of chronic bronchitis and emphysema is, however, much more commonly seen than either of the two individual syndromes.

Emphysema in young adults, mainly affecting the lower lobes, may be associated with genetically determined α_1-antitrypsin deficiency in the serum.

Clinical Features. Most patients with pulmonary emphysema complain of exertional dyspnoea, but since other causes of airway obstruction, such as chronic bronchitis and bronchial asthma, often co-exist, it is seldom possible to assess the contribution of emphysema *per se* to the production of this symptom. In patients with chronic bronchitis and emphysema there is a progressive increase in respiratory disability, but the tempo of deterioration varies widely from one case to another. For example, in patients with a relatively minor component of chronic bronchitis the exertional dyspnoea increases slowly over a period of several years, but the course of the disease tends to be more rapid where chronic bronchitis and respiratory infection are major aetiological factors. Other important differences between these two contrasting forms of chronic bronchitis and emphysema are shown in Table 7.

The *physical signs* which may be observed in emphysema are summarised in Table 4 (p. 326). Other clinical abnormalities recorded in this condition (many of which are due to chronic airway obstruction) include (1) a reduction in the length of the trachea palpable above the sternal notch, (2) tracheal descent with inspiration, (3) contraction of the sternomastoid and scalene muscles on inspiration, (4) excavation of the suprasternal and supraclavicular fossae during inspiration, (5) jugular venous filling during expiration, (6) indrawing of the costal margins during inspiration, and (7) an increase in the antero-posterior diameter of the chest relative to the lateral diameter.

Radiological Features. A firm diagnosis of emphysema cannot be made by radiological examination alone, but the following abnormalities suggest that it may be present:

1. Unusually translucent lung fields, with loss of peripheral vascular markings.
2. Bullae (p. 393).
3. A low flat diaphragm, which moves poorly on fluoroscopy (2 cm or less).
4. Abnormal prominence of the pulmonary arterial shadows at both hila.

Abnormalities caused by pulmonary infection ('inflammatory shadowing') may also be present, especially in patients with an important degree of chronic bronchitis. In the late stages, when pulmonary hypertension and right ventricular failure supervene, there is enlargement of the main pulmonary artery, the right ventricle and atrium, and ultimately all cardiac chambers.

Pulmonary Function Tests. See page 388.

Diagnosis. It is important to exclude unrelated or remediable causes of dyspnoea in patients suspected of having emphysema. These are (1) *left-sided cardiac failure* due to hypertension or to valvular or ischaemic heart disease, in which crepitations from pulmonary oedema may be wrongly ascribed to bronchitis; (2) *spontaneous pneumothorax*, the physical signs of which may pass unnoticed in the presence of emphysema; and (3) *giant bullae*, which may be the main cause of dyspnoea in a patient with only a mild or moderate degree of emphysema. In order to exclude these conditions, radiological examination

TABLE 7

Chronic Bronchitis and Emphysema

	Predominant Abnormality	
	Chronic Bronchitis	Emphysema
Age	Middle-aged	Elderly
Build	Thick-set	Slender
Degree of bronchitis	Severe	Mild
Episodes of bacterial infection	Frequent	Occasional
Duration of exertional dyspnoea	Fairly short (2-5 years)	Long (5-20 years)
Degree of exertional dyspnoea	Variable but seldom severe	Slowly progressive but eventually severe
Central cyanosis	Moderate or severe	Slight or absent
Rhonchi	Numerous	Few
Pa_{O_2}	Markedly reduced (60-30 mm Hg)	Slightly reduced at rest (> 60 mm Hg)
Pa_{CO_2}	Always increased (50-90 mm Hg)	Normal or slightly increased (40-50 mm Hg)
Residual volume	Slightly increased	Markedly increased
Gas transfer factor (Tco)	Usually normal	Usually decreased
X-ray chest	'Emphysema' slight or absent 'Inflammatory shadowing' often present	'Emphysema' marked 'Inflammatory shadowing' slight or absent
ECG	Pattern of right ventricular hypertrophy relatively common	Often normal
Right ventricular failure	Early	Late

should be undertaken whenever an emphysematous patient experiences a rapid increase in dyspnoea.

Bronchial carcinoma, *pneumoconiosis* and *pulmonary tuberculosis* can be excluded by radiography and bacteriological examination. Pneumoconiosis confers certain pension rights, and in any suspected case a detailed occupational history should always be taken.

Complications

1. *Ventilatory failure* (p. 323); *secondary polycythaemia* (p. 742).
2. *Pulmonary hypertension* and *right ventricular failure* are the inevitable end-results of chronic bronchitis and emphysema. The increase in pulmonary arterial pressure is due to vasoconstriction mediated by the effect of hypoxia on pulmonary arterioles and ultimately to destruction of the pulmonary vascular bed. As hypoxia is aggravated by any increase in the degree of airway obstruction, bacterial infection in the respiratory tract, oedema of the bronchial mucosa, oversecretion of bronchial mucus and spasm of the bronchial muscles (which can all cause hypoxia) are liable to increase the pulmonary arterial pressure and precipitate right ventricular failure. Conversely, effective treatment of these causes of hypoxia, combined with oxygen therapy (p. 330) and diuretics (p. 195) may relieve pulmonary hypertension and cardiac failure, at least for a time.
3. *Pulmonary bullae*, single or multiple, large or small, may develop in emphysematous lung tissue, regardless of the primary pathology. Bullae are inflated thin-walled spaces created by rupture of the alveolar walls. They are usually situated subpleurally, and are commonly found along the anterior borders of the lungs. A small bulla may rupture, causing *spontaneous pneumothorax*. In other circumstances bullae may increase progressively in size, and eventually become so large that they interfere seriously with pulmonary ventilation.

Treatment. There is no specific remedy for emphysema, but the patient may benefit considerably from the treatment of associated chronic bronchitis (p. 389), and ventilatory failure (p. 332), which is a common complication. Obesity must be prevented or corrected, as excess weight is an intolerable burden on the reduced cardiorespiratory reserve. Breathing exercises of the traditional type, encouraging the patient to force air out of his lungs, are of no value; indeed, by increasing air trapping, they may even be harmful. If physiotherapy in emphysema has any purpose at all, it should be to induce relaxation of the cervical muscles and to show the patient how to expire slowly and steadily through pursed lips. The surgical ablation of giant bullae, where this is feasible, may allow relatively normal lung tissue compressed by the bullae to re-expand and this may bring about a dramatic improvement in pulmonary function.

BRONCHIECTASIS

Aetiology and Pathogenesis. Bronchiectasis, which is the term used to describe abnormal dilatation of the bronchi, may be produced in three different ways:

1. When pulmonary collapse follows obstruction of groups of *small* bronchi by secretion, the shrinkage of the affected portion of lung exerts outward traction

on the walls of the medium-sized bronchi, which become dilated. Bronchiectasis arising in this way may be reversible if the obstructed bronchi can be cleared of secretion before the walls of the dilated bronchi are seriously damaged by infection. When the bronchial obstruction is itself the result of severe bronchopulmonary infection the bronchiectasis is liable to become permanent. It is probable that damage to the deeper layers of the bronchial walls, such as occurs in all types of suppurative pneumonia and lung abscess, and in some cases of pulmonary tuberculosis and acute lobular pneumonia, is much more important in this respect than the relatively superficial lesions of acute bronchitis.

2. It may be due to bronchial distension resulting from the formation of pus beyond a lesion obstructing a major bronchus, such as a bronchial carcinoma, a tuberculous hilar lymph node or an inhaled foreign body.

3. Rarely, it may be the result of congenital maldevelopment of the bronchi.

Bronchial dilatation by itself does not necessarily cause symptoms, which are usually due to infection in the dilated bronchi and in the related lung tissue.

Because of the many different causes of bronchiectasis no precise age incidence can be stated. When it occurs following acute pulmonary infections or secondary to obstruction of a bronchus by tuberculous lymph nodes (the two most common causes), the disease usually starts in childhood but may not produce severe symptoms until some years later.

Pathology. The bronchial dilatations may be cylindrical, fusiform or saccular in shape. Although bronchiectasis may involve any part of the lungs, depending on the site of the primary pathological process, the lower lobes are more frequently affected than the upper and middle. In addition, the more efficient drainage by gravity of the upper lobes renders bronchiectasis there less liable to produce serious symptoms than when it involves the lower lobes. The bronchiectatic cavities may be lined by granulation tissue, squamous epithelium or normal ciliated epithelium, depending on the degree of infection present. There may also be inflammatory changes in the deeper layers of the bronchial walls and chronic inflammatory and fibrotic changes in the surrounding lung tissue.

Clinical Features. Three groups of clinical features occur in bronchiectasis:

1. *Those due to the accumulation of pus in the bronchiectatic cavities:*

(*a*) *Chronic cough*, usually worse in the mornings and often induced by changes in posture.

(*b*) *Purulent sputum*, which in advanced cases is copious and sometimes foetid.

2. *Those due to inflammatory changes in the surrounding lung tissue and pleura:*

(*a*) *Febrile episodes*, commonly ascribed to influenza or pneumonia, which often follow an upper respiratory infection and usually last for a few days but occasionally for weeks. Malaise, shivering and sleep sweating accompany the pyrexia, and there is almost always an increase in the amount of cough and sputum. A neutrophil leucocytosis is usually present.

(*b*) *Dry pleurisy*, which frequently accompanies the febrile episodes.
(*c*) *Empyema*, which is an occasional complication of bronchiectasis.

When suppuration, either in the dilated bronchi or in the lungs, is a marked feature it causes a decline in the patient's general health, with lassitude, anorexia, loss of weight, sleep sweating and clubbing of the fingers and toes. In many cases, however, symptoms are slight, consisting merely of recurrent episodes of cough and purulent sputum with no symptoms in the intervening periods and no deterioration in general health.

3. *Haemoptysis*, caused by bleeding from thin-walled anastomotic vessels connecting the pulmonary and bronchial arteries, and situated in the walls of the bronchiectatic cavities. It ranges in amount from blood-stained sputum to massive haemorrhage. It may be present in association with the first two groups of symptoms, but recurrent haemoptysis may also occur as an isolated symptom in the absence of cough and sputum ('dry' bronchiectasis).

Physical Signs in the Chest. These may be unilateral or bilateral and are usually basal. If the bronchiectatic cavities are dry and there is no collapse, there may be *no* abnormal physical signs. If a large amount of secretion is present, numerous coarse crepitations are heard over the affected areas. When collapse is present the character of the physical signs depends on whether or not the major bronchi in the collapsed lobe are patent. The signs found in both circumstances are described on page 396.

Radiological Examination. In ordinary radiographs the dilated bronchi themselves are seldom visible, but radiological changes may be produced by associated pulmonary inflammation or collapse. A diagnosis of bronchiectasis can be made with certainty only by bronchographic examination.

Diagnosis. When bronchograms are available the diagnosis of bronchiectasis is self-evident, but it should not be forgotten that other conditions, notably chronic bronchitis and active pulmonary tuberculosis, may co-exist. It is of particular importance, when surgical treatment for bronchiectasis is contemplated, to consider whether the symptoms may not be principally due to chronic bronchitis. This should always be suspected when dyspnoea, wheeze and rhonchi are prominent features.

Bacteriological examination of the sputum is necessary in every case to exclude tuberculosis and to identify pathogenic bacteria.

Course and Prognosis. With antibiotic therapy the prognosis, even in advanced cases, has greatly improved and the incidence of complications such as pneumonia, empyema, cerebral abscess and amyloidosis has fallen considerably.

Prophylaxis. As bronchiectasis commonly starts in childhood following measles, whooping-cough or a primary tuberculous infection, it is essential that these conditions receive adequate treatment. The early recognition and treatment of bronchial obstruction (p. 396) is particularly important in this respect.

Treatment. POSTURAL DRAINAGE. The purpose of this measure is to keep the dilated bronchi emptied of secretion. Efficiently performed it is of great value both in reducing the amount of cough and sputum and in preventing the 'toxaemia' caused by retained sputum and associated bronchopulmonary infection. In its simplest form, postural drainage consists of adopting a position in which the lobe to be drained is uppermost, so as to allow secretions in the dilated bronchi to gravitate towards the trachea, from which they can readily be cleared by vigorous coughing. The optimum duration and frequency of postural drainage depends on the amount of sputum, but 5 to 10 minutes twice daily is adequate in most cases.

CHEMOTHERAPY. The policy governing the use of antibiotics in bronchiectasis is the same as that in chronic bronchitis (p. 389).

SURGICAL TREATMENT. Before a decision can be made for or against surgical treatment it is essential to obtain bronchograms demonstrating exactly the extent of the bronchiectasis. For this purpose the bronchi of all segments of *both* lungs must be outlined with a radio-opaque contrast medium. Pulmonary function should also be assessed.

The use of antibiotics has greatly reduced the need for surgical treatment. Unfortunately many of the cases in which medical treatment has been unsuccessful are also unsuitable for surgical treatment either because the bronchiectasis is too extensive or because most of the symptoms are due to co-existing chronic bronchitis. Emphysema of even moderate severity is a contraindication to surgical treatment, as the increase in exertional dyspnoea which inevitably results is more distressing to the patient than the symptoms of bronchiectasis. The most favourable cases for surgery are children and young adults in whom the bronchiectasis is confined to a single lobe or part of a lobe. Lobar or segmental resection in these patients is a highly satisfactory operation, carrying little risk.

In all cases treated surgically the risks of operation are materially increased by the presence of a large amount of sputum. Efficient pre-operative treatment with postural drainage and chemotherapy is thus of great importance.

OTHER MEASURES. Chronic sepsis in the nose, mouth and pharynx should be treated, and anaemia should be corrected.

BRONCHIAL OBSTRUCTION AND ITS CONSEQUENCES

When a large bronchus is *completely obstructed*, the air in the lung, lobe or segment it supplies is absorbed, the alveolar spaces close, and the affected portion of lung tissue contracts and becomes solid (*absorption collapse*). The percussion note over the collapsed lung or lobe is dull, the breath sounds are diminished or absent, and radiological examination shows displacement of the trachea and/or heart shadow towards the side of the lesion, elevation of the diaphragm on the same side and a dense pulmonary opacity of characteristic size, shape and position (Fig. 58). If the collapse involves a smaller portion of lung (e.g. the right middle lobe or a bronchopulmonary segment), displacement of the mediastinum may not occur, and abnormal physical signs may be difficult to detect, but a characteristic radiographic opacity will be present. The radiological features of pulmonary collapse are shown in Figure 59. Semi-solid material, such as mucus, mucopus or blood clot, obstructing a large bronchus is apt to fragment, and portions of it may then be aspirated into the peripheral bronchi, leaving the larger bronchus clear. The diminished or absent breath sounds are then replaced by bronchial breath sounds, but the other clinical or radiological abnormalities do not change.

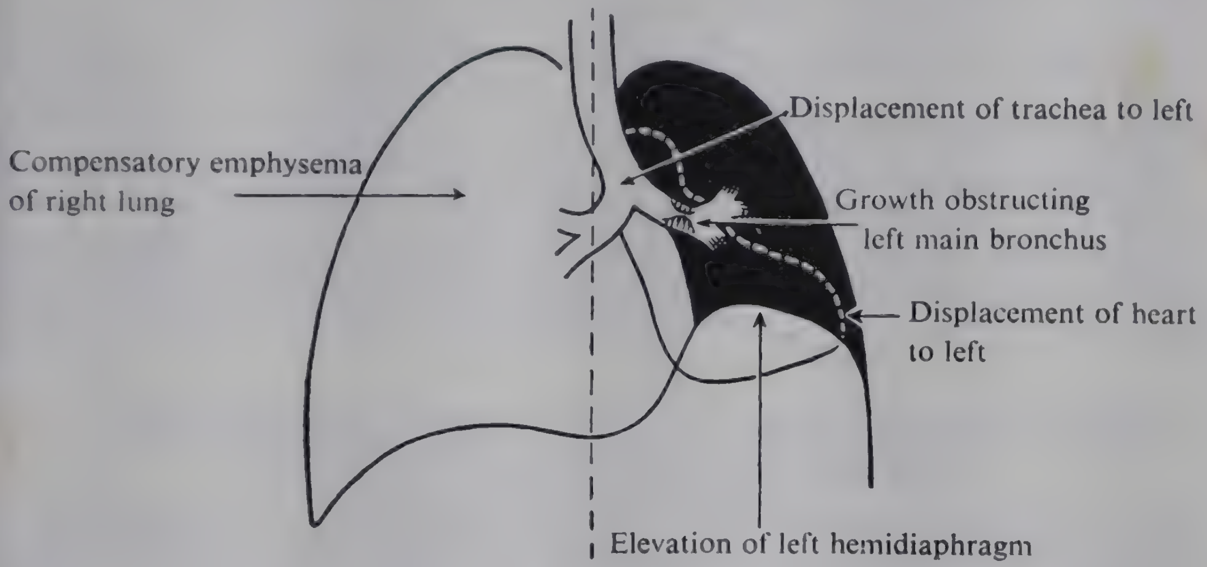

Displacement of trachea to left
Compensatory emphysema of right lung
Growth obstructing left main bronchus
Displacement of heart to left
Elevation of left hemidiaphragm

FIG. 58

THE EFFECTS ON NEIGHBOURING STRUCTURES OF COLLAPSE OF THE LEFT LUNG

If a large bronchus is *partially obstructed*, a situation occasionally arises in which there is less resistance to air flow through the narrowed bronchus during inspiration than during expiration, when the obstruction may become temporarily complete. This differential between inspiratory and expiratory airway resistance, which is increased by coughing, results in overdistension of the lung, lobe or segment supplied by the partially obstructed bronchus (*obstructive emphysema*). The percussion note over such a lesion is resonant or hyper-resonant, and the breath sounds are diminished. A chest radiograph shows hypertranslucency of the affected part of lung, and on fluoroscopic examination the mediastinum can be seen to move towards the opposite side of the chest during expiration, because the pressure within the affected lung then exceeds that within the contralateral lung.

Causes of Bronchial Obstruction. The lesions most likely to obstruct a large bronchus are:

1. Tumours, e.g. bronchial carcinoma (p. 401) or adenoma (p. 404).
2. Enlarged tracheobronchial lymph nodes, malignant or tuberculous.
3. Inhaled foreign bodies.

4. Bronchial casts or plugs, consisting of inspissated mucus or blood clot.
5. Collections of mucus or mucopus retained in the bronchi as a result of ineffective expectoration.

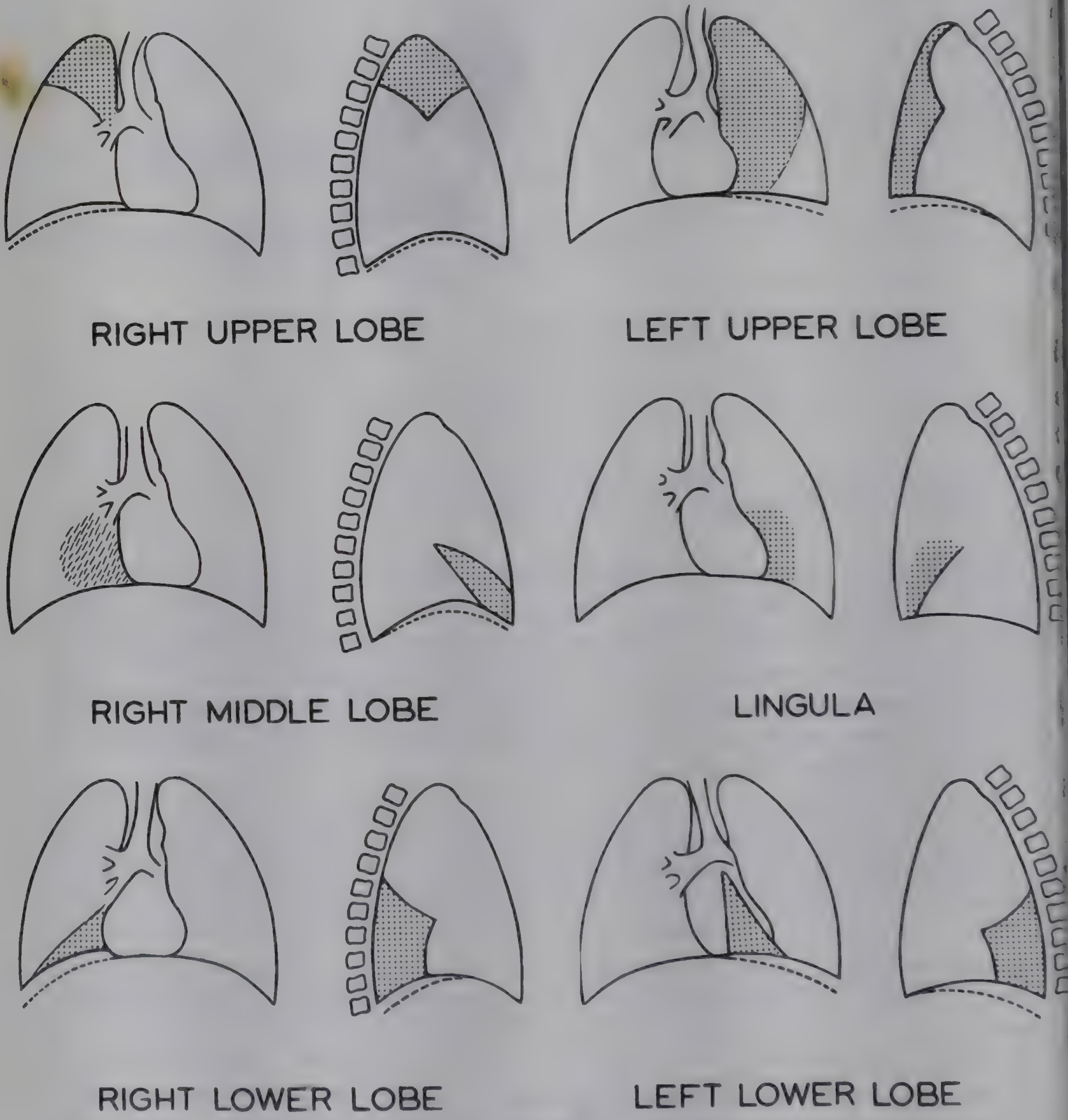


FIG. 59

RADIOLOGICAL FEATURES OF PULMONARY COLLAPSE CAUSED BY BRONCHIAL OBSTRUCTION

The dotted line represents the normal position of the diaphragm.

Rare causes of bronchial obstruction include congenital bronchial atresia, fibrous bronchial stricture (often post-tuberculous), aortic aneurysm, giant left atrium and pericardial effusion.

Effects of Bronchial Obstruction. Whenever a bronchus is narrowed, bacterial infection of the lung tissue it supplies is virtually inevitable, and this may occur even when the degree of obstruction is insufficient to cause pulmonary collapse. This explains why pneumonia may be the first clinical manifestation of bronchial carcinoma. The infection is usually of low virulence, but in some cases severe pulmonary suppuration (p. 349) may occur, with empyema (p. 418) as a further complication.

Bronchial obstruction impairs pulmonary function, but this is unlikely to produce symptoms unless a main or lobar bronchus is involved, or if the patient's overall pulmonary function is so poor that obstruction of a smaller bronchus critically diminishes the respiratory reserve. Sudden occlusion of a main or lobar bronchus by mucus or mucopus occurring as a post-operative complication may cause severe dyspnoea and hypoxia.

Clinical Manifestations in Bronchial Obstruction

1. **Tumours.** Bronchial obstruction by a carcinoma usually produces pulmonary collapse at an early stage, and seldom causes obstructive emphysema. Pulmonary infection is common, and this may be complicated by empyema. The degree of exertional dyspnoea produced by a bronchial carçinoma is directly related to the size of the obstructed bronchus. The rate of growth of a bronchial adenoma is much less rapid than that of a carcinoma. Complete bronchial obstruction and pulmonary collapse are therefore later developments in the presence of an adenoma, and obstructive emphysema, caused by partial bronchial obstruction, may be observed during the intervening period.

2. **Enlarged Tracheobronchial Lymph Nodes.** By compressing or invading the bronchial wall, enlarged lymph nodes may produce the same clinical manifestations of bronchial obstruction as a tumour within the lumen, and in bronchial carcinoma both types of lesion may co-exist. Bronchial obstruction by enlarged lymph nodes in Hodgkin's disease and other forms of reticulosis is less common than in bronchial carcinoma, presumably because these are less invasive types of tumour. In children with severe primary tuberculous infection large caseous tracheobronchial lymph nodes may compress and erode lobar or segmental bronchi, occasionally even a main bronchus. Caseous material and granulation tissue from the lymph node may be extruded into the bronchial lumen to increase the degree of bronchial obstruction. Tuberculous infection may develop in the collapsed lobe or segment, and later complications include bronchial stricture and bronchiectasis. In all these conditions the supraclavicular lymph nodes may also be involved, and biopsy of one of these nodes may provide a positive histological diagnosis of tumour, reticulosis or tuberculosis.

3. **Foreign Bodies.** An inhaled foreign body generally lodges in the right main, intermediate or lower bronchus, as these bronchi are almost directly in line with the trachea. Children inhale foreign bodies more often than adults. These include nuts (usually peanuts), peas, beans and small pieces of metallic or plastic

toys. Adults, on the other hand, are more likely to inhale fragments of tooth during extractions under general anaesthesia, and pieces of mutton or rabbit bone. When a foreign body becomes impacted in a bronchus, it first produces, after an initial episode of choking, either obstructive emphysema or absorption collapse, and a persistent low-pitched rhonchus may be audible all over the chest. Within a few days pathogenic bacteria, carried into the respiratory tract with the foreign body, give rise to a suppurative pneumonia in the collapsed lobe. The patient at this stage often has a high temperature, cough productive of purulent sputum, and pleural pain. On clinical examination there may be a pleural rub and physical signs of either pulmonary collapse or consolidation. Radiological examination shows either obstructive emphysema or collapse and/or pneumonic consolidation of the lobe or lobes supplied by the obstructed bronchus.

4. **Bronchial Casts or Plugs.** These may consist of either inspissated mucus or blood clot. Plugs of mucus may cause bronchial obstruction in patients with asthma (p. 377) or allergic bronchial aspergillosis (p. 372). Secondary bacterial infection of the collapsed lung may occur, but is seldom severe. Bronchial obstruction by blood clot frequently follows severe haemoptysis, but as this complication is usually recognised and treated at an early stage, secondary bacterial infection of collapsed lung tissue seldom occurs.

5. **Retained Secretions.** A main, lobar or segmental bronchus may be obstructed by retained mucus or mucopus when a patient is unable to cough effectively because of chest pain, muscular weakness or general debility. Pulmonary collapse following an upper abdominal or thoracic operation, or an injury to the chest wall, is due to this type of bronchial obstruction. Secondary bacterial infection of the collapsed lung tissue supervenes at an early stage, but this generally responds rapidly to treatment with an appropriate antibiotic (p. 329) after the bronchial obstruction has been relieved by vigorous postural drainage and, if necessary, by bronchoscopic aspiration of the obstructing secretions.

Post-operative pulmonary collapse can usually be prevented by forbidding patients to smoke for three weeks prior to operation, by vigorous pre- and post-operative breathing exercises, and by regularly supervised coughing during the immediate post-operative period.

Diagnosis and Treatment of Bronchial Obstruction

The cause of the bronchial obstruction can be discovered by bronchoscopic examination, and in the case of tumour and tuberculosis histological confirmation of the diagnosis can usually be obtained by bronchial biopsy. Foreign bodies can be extracted by bronchoscopy or bronchotomy. If bronchial casts, plugs or secretions cannot be dislodged by postural coughing, they should be removed through a bronchoscope. In other forms of bronchial obstruction the treatment is that of the primary condition.

Hyaline Membrane Disease

(RESPIRATORY DISTRESS SYNDROME)

This condition merits a brief addendum, as it is an important cause of pulmonary collapse in premature infants, in whom it is a common cause of death. In fatal cases the terminal bronchioles and alveolar ducts are lined by an eosinophilic hyaline membrane, but the significance of this finding is not yet fully understood. A deficiency of pulmonary surfactant (a lipoprotein which normally lines the alveoli and which, by lowering surface tension, prevents apposition of the alveolar walls) may be the basic cause of this syndrome. If that is the case, the 'hyaline membrane' may consist merely of a fibrinous transudate drawn from the pulmonary capillaries by the highly negative intrathoracic pressure.

Respiratory distress becomes apparent within a few hours of birth. There is a rapid increase in respiration rate, with inspiratory retraction of the chest wall and expiratory grunting. Progressive cyanosis and death follow within 48 hours in about 50 per cent of cases, the mortality being higher in the more premature infants.

Treatment consists of the administration of oxygen, if necessary by intermittent positive-pressure ventilation, which may be essential to control hypercapnia. Spontaneous breathing against a positive pressure of 5-10 cm of water may help to prevent alveolar collapse during expiration. Metabolic acidosis must be corrected by the infusion of bicarbonate. Continuous monitoring of the Po_2, Pco_2 and pH of umbilical arterial blood is essential in severe cases.

INTRATHORACIC TUMOURS

Tumours of Bronchus and Lung

Primary. Bronchial carcinoma is by far the most common malignant pulmonary tumour. Benign tumours are rare.

Secondary. A primary carcinoma in any organ, but particularly in breast, kidney, uterus, ovary, testis, thyroid or in lung itself may give rise to pulmonary metastatic deposits, as may an osteogenic or melanotic sarcoma.

Bronchial Carcinoma

Bronchial carcinoma accounts for almost 40 per cent of all male deaths from malignant disease. It is five times more common in men than in women, and occurs most frequently between the ages of 50 and 75. Cigarette smoking is responsible for most cases of bronchial carcinoma, and the increased risk is directly proportional to the amount smoked. For example, the death rate from the disease in heavy cigarette smokers is 30 times that in non-smokers. The death rate is slightly higher in urban than in rural dwellers, presumably because of the effects of atmospheric pollution. There is also a higher incidence in certain occupations (p. 411).

Pathology. The tumour, which may be a squamous or 'oat-cell' (undifferentiated) carcinoma or, occasionally, an adenocarcinoma, arises from bronchial epithelium or mucous glands and at an early stage may occlude the bronchial lumen. It also invades the deeper layers of the bronchial wall and the surrounding lung tissue. When the tumour obstructs a major bronchus it causes pulmonary collapse and infection (p. 396). A tumour arising from a peripheral bronchus may attain a very large size without producing a significant degree of collapse. Necrosis in a tumour of this type may give rise to a 'carcinomatous lung abscess'.

The tumour may involve the pleura either directly or by lymphatic spread, causing a pleural effusion which is often blood-stained. It may also invade the chest wall and cause severe pain by irritation of the intercostal nerves or the brachial plexus. The tumour or its lymph node metastases may extend into the mediastinum, involving the phrenic and recurrent laryngeal nerves, the sympathetic trunk, the superior vena cava, the pericardium and myocardium, the trachea and the oesophagus.

Lymphatic spread may occur to the supraclavicular and occasionally to the axillary lymph nodes as well as to the mediastinal lymph nodes and pleura. Blood-borne metastases occur most commonly in liver, bone, brain, suprarenals, skin and kidneys. Even a small primary tumour may cause widespread metastases.

Clinical Features. The onset is usually insidious. Cough is the most common early symptom. The amount and character of the sputum depend on the degree of secondary infection present. Repeated slight haemoptysis is a common and characteristic feature. Dyspnoea may occur early when a lobe or lung is collapsed, but in other circumstances is a late symptom unless the patient is coincidentally suffering from chronic bronchitis and emphysema. Pulmonary infection beyond an obstructing tumour gives rise to pneumonia which is unusually slow to respond to treatment. Pleural pain is a frequent symptom and may be due either to infective pleurisy or to malignant invasion of the pleura. A small pleural effusion in a patient with a bronchial carcinoma is often due to infection but a massive blood-stained effusion is almost invariably due to invasion of pleura by tumour. Pain in the chest wall or in an upper limb with a nerve root distribution may be present if the tumour involves intercostal nerves or the brachial plexus. An apical bronchial carcinoma may cause Horner's syndrome (p. 825). Rib destruction often accompanies these nerve lesions.

The symptoms and signs which may occur when the tumour invades the mediastinum are described in the section on mediastinal tumours (p. 405).

Occasionally the presenting symptom is due to a metastatic deposit, e.g. epileptiform fits or personality change (cerebral metastasis), pathological fracture (skeletal metastasis), haematuria (renal metastasis), skin nodules, usually tender (cutaneous metastases). Clubbing of the fingers is often seen and a few patients present the features of hypertrophic pulmonary osteoarthropathy, peripheral neuropathy (p. 897), or cerebellar degeneration, none of these manifestations necessarily being related to the presence of metastatic tumour. Rarely an oat-cell carcinoma may act as an ectopic source of adrenocorticotrophic, antidiuretic or other hormone, and the patient may present with symptoms and signs of endocrine dysfunction (p. 656). Lassitude, anorexia and loss of weight are *late* symptoms except when pulmonary suppuration is an early development.

Physical Signs in the Chest. These depend on the size of the tumour, but even more on the nature and extent of its secondary effects on lung and pleura.

1. In the early stages a tumour may cause no abnormal physical signs whatever.
2. A tumour obstructing a large bronchus produces the physical signs of collapse or obstructive emphysema (p. 397).
3. A massive tumour may give rise to signs resembling those of a pleural effusion.
4. Involvement of the pleura either by infection or by tumour may produce signs of dry pleurisy (p. 414) or of a pleural effusion (p. 415).

Radiological Examination. A bronchial carcinoma may cause any of the following radiological abnormalities:

1. A dense, irregular, hilar opacity.
2. A dense, fairly well circumscribed, peripheral pulmonary opacity, usually large when first discovered, sometimes irregularly cavitated.
3. An opacity consistent with collapse of a whole lung, a lobe or a segment. This may or may not be associated with a dense, irregular, hilar opacity due to the tumour itself.

In some cases radiological examination may also show a pleural effusion (indicating either infection or secondary tumour in the pleura), broadening of the mediastinal shadow (due to lymph node metastases), osteolytic lesions of the ribs (indicating either direct invasion by tumour or blood-borne metastases) or unilateral diaphragmatic paralysis (indicating involvement of the phrenic nerve). A paralysed hemidiaphragm is usually raised and on fluoroscopy moves 'paradoxically' when the patient sniffs, i.e. it moves upwards instead of downwards.

Bronchoscopy. Inspection of the intrabronchial portion of the tumour and removal of tissue for histological examination is possible in about 60 per cent of cases. In this way the diagnosis can be established with certainty, often at an early and curable stage. Bronchoscopic examination may also indicate the extent of the tumour, which has an important bearing on the patient's suitability for surgical treatment.

Diagnosis. The diagnosis of bronchial carcinoma should be considered in all middle-aged or elderly persons, particularly cigarette smokers, who complain of respiratory symptoms of recent onset which do not clear up completely within a period of two weeks, particularly if haemoptysis or pleural pain is present. Radiological examination should be carried out in all such cases, followed by bronchoscopy whenever the radiological appearances are at all suggestive of tumour. A normal chest radiograph does not exclude a diagnosis of bronchial carcinoma in a patient presenting with haemoptysis, and bronchoscopy is indicated in these cases also. Examination of the sputum for malignant cells is a valuable diagnostic measure when practised by a pathologist with special interest and experience in this procedure, but in other circumstances the results can be seriously misleading.

The differential diagnosis includes chronic bronchitis, bronchiectasis, slowly resolving pneumonia, lung abscess, pulmonary tuberculosis, aspergilloma (p. 372), primary mediastinal tumour and metastatic pulmonary tumour. Sputum examination is essential in all cases to exclude tuberculosis. It should not be forgotten that tuberculosis and carcinoma may co-exist.

Course and Prognosis. Unless surgical treatment is practicable the average period of survival after the diagnosis is made is less than one year.

Treatment. Resection of the lung (pneumonectomy) or, in selected cases, of the lobe containing the tumour (lobectomy) offers the best prospect of survival. The operation can be performed only on the small number of cases (about 20 per cent) in which the tumour is discovered at an early and relatively localised stage and pulmonary function is adequate. The tumour is liable to recur even after an apparently satisfactory operation, and only 30 per cent of such patients survive for more than five years. Early diagnosis provides slightly better results, but the prognosis depends to an even greater extent on the histological type of tumour and on the presence or absence of metastatic deposits in the hilar lymph nodes. The outlook is particularly unfavourable when the tumour is an oat-cell carcinoma.

Small tumours can occasionally be eradicated by X-ray therapy, but this form of treatment is more often used to relieve distressing complications such as superior vena caval obstruction, recurrent haemoptysis and pain caused by chest wall invasion or by skeletal metastatic deposits. Obstruction of the trachea and main bronchi can also be relieved temporarily by irradiation, but as the latter may initially produce tumour swelling and a dangerous increase in the degree of obstruction, a cytotoxic drug, e.g. mustine hydrochloride intravenously, should be given first. Cytotoxic drugs, given alone, are in general less effective than radiotherapy for palliative treatment, except in the case of malignant pleural effusion (p. 417).

Bronchial Adenoma

This is an uncommon tumour occurring in a younger age group than carcinoma and affecting females as often as males. Although classified as a benign tumour it possesses some of the properties of a malignant growth and may eventually give rise to metastases. A bronchial adenoma of the 'carcinoid' type may secrete 5-hydroxytryptamine or a related substance, and give rise to the carcinoid syndrome (p. 507). The usual pathological lesion is a small, vascular tumour within the bronchial lumen with a large encapsulated extrabronchial extension.

The main clinical features, which may have a duration of several years, are recurrent haemoptysis, due to the vascularity of the tumour, recurrent pulmonary infection resulting from bronchial obstruction and, in rare cases, the carcinoid syndrome. The physical signs most frequently found are those of collapse. The diagnosis from bronchial carcinoma can be made only by bronchoscopy and histological examination of a portion of the tumour.

Treatment consists of resection of the pulmonary lobe or segment containing the tumour along with the bronchus from which it arises.

Secondary Tumours of the Lung

Blood-borne metastatic deposits in the lungs may be derived from malignant disease anywhere in the body. The usual sites of the primary tumour have already been stated (p. 401). The secondary deposits are usually multiple and bilateral. Haemoptysis occurs in some cases but often there are no respiratory symptoms and the diagnosis is made by radiological examination.

Extensive infiltration of the pulmonary lymphatics by tumour may develop in patients with carcinoma of breast, stomach, pancreas or bronchus. This condition, known as *pulmonary lymphatic carcinomatosis*, causes severe and rapidly progressive dyspnoea.

Tumours of the Mediastinum

Classification

Tumours of the lymph nodes:

1. Secondary carcinoma, usually from bronchus or breast.
2. Reticulosis, including Hodgkin's disease.
3. Lymphosarcoma.
4. Leukaemia.

Thymic tumours, e.g. malignant thymoma.

Connective tissue tumours, e.g. fibroma, lipoma (benign); sarcoma (malignant).

Neural tumours, e.g. neurofibroma.

Developmental tumours and cysts, e.g. teratoma; dermoid, bronchogenic and pleuro-pericardial cysts.

Other lesions presenting as mediastinal tumours, e.g. aortic aneurysm, aneurysmal dilatation of left atrium, intrathoracic goitre, sarcoidosis involving lymph nodes.

Pathology and Clinical Features

BENIGN TUMOURS. The conditions in this category include neural tumours, teratoma, developmental cysts and intrathoracic goitre. All of them are rare. The effects produced by a benign tumour are related mainly to its size, and symptoms are present only when it compresses vital structures. The diagnosis of benign tumour is usually made by chance, when radiological examination of the chest is undertaken for some other reason. Many of the cases are found by mass radiography. If a tumour becomes very large it may cause dyspnoea by compression of lung tissue, or occasionally by narrowing the trachea. A benign tumour in the upper part of the thorax occasionally compresses the superior vena cava (p. 406). Invasion of mediastinal structures, bronchi or lungs never occurs.

MALIGNANT TUMOURS. Included in this category are mediastinal lymph node metastases, reticulosis, lymphosarcoma, leukaemia, malignant thymic tumours, mediastinal sarcoma and, in addition, aortic and innominate aneurysms which have certain features in common with malignant mediastinal tumours. All these conditions, except lymph node metastases, are uncommon.

The distinguishing feature of this group of tumours is their power to invade as well as to compress mediastinal structures, bronchi and lungs. As a result of this property even a small malignant tumour can produce symptoms, although as a rule the tumour has attained a considerable size before this happens.

The structures which may be invaded or compressed and the symptoms and signs produced in each case are:

(*a*) *Trachea:* dyspnoea, stridor, brassy cough.
(*b*) *Main bronchus:* pulmonary collapse, dyspnoea.
(*c*) *Oesophagus:* dysphagia.
(*d*) *Phrenic nerve:* diaphragmatic paralysis (p. 403).
(*e*) *Left recurrent laryngeal nerve:* paralysis of left vocal cord, hoarseness.
(*f*) *Sympathetic trunk:* Horner's syndrome (p. 825).
(*g*) *Pericardium:* pericarditis, either *dry* with pericardial rub, or *with effusion*.
(*h*) *Superior vena cava:* oedema and cyanosis of head and neck, and sometimes of upper limbs also, with distension of external jugular veins and dilated anastomotic veins on anterior chest wall and in axillary regions.

Radiological Examination. A *benign mediastinal tumour* generally appears as a large, round, sharply circumscribed opacity, situated mainly in the mediastinum but often encroaching on one or both lung fields.

A *malignant mediastinal tumour* seldom has a clearly defined margin and often presents as a general broadening of the mediastinal shadow.

Diagnosis. The only common mediastinal tumour is that produced by lymph node metastases from a bronchial carcinoma. An aortic aneurysm and an intrathoracic goitre can often be recognised from the other clinical features, and leukaemia from the blood picture, and a diagnosis of sarcoidosis, reticulosis or lymphosarcoma can often be made from biopsy of a superficial lymph node. The known radiosensitivity of the reticuloses is sometimes used as a diagnostic test, rapid shrinkage of the tumour following radiotherapy being a typical feature.

As bronchial carcinoma is such a common primary cause of mediastinal tumour, bronchoscopy should be carried out in all cases. If enlarged mediastinal lymph nodes are suspected one of these can be removed for histological examination by the technique of mediastinoscopy (p. 328). In some cases, however, an exact diagnosis cannot be made without surgical exploration of the chest and removal of the tumour or a portion of it for histological examination.

Treatment. *Benign Mediastinal Tumours.* These should be removed surgically as soon as they are discovered because (*a*) they tend to produce symptoms sooner or later and (*b*) some of them, particularly cysts, may become infected while others, especially neural tumours, may undergo malignant change. The operative mortality is very small.

Malignant Mediastinal Tumours. In reticulosis, lymphosarcoma, leukaemia and malignant thymoma, radiotherapy often produces a remarkable clinical improvement by reducing the size of the tumour. The improvement, although only temporary, may last for months or even years. Lymph node metastases from bronchial carcinoma sometimes respond fairly well to radiotherapy, which may provide valuable symptomatic relief. Complications such as superior vena caval and tracheal obstruction can often be relieved in this way.

INTERSTITIAL LUNG DISEASE

This term is applied to a group of pulmonary diseases which have the following features in common:

1. Thickening of the alveolar walls by oedema, cellular exudate or fibrosis.
2. Increased stiffness of the lungs (reduced compliance), associated with exertional dyspnoea.
3. A combination of pulmonary ventilation-perfusion imbalance and gas transfer defect, leading to hypoxia, hyperventilation and hypocapnia.

Aetiology. Interstitial lung disease is caused by several aetiologically distinct pathological processes, but these all give rise to similar symptoms, physical signs, radiological changes and disturbances of pulmonary function. They are thus worthy of collective consideration. The most frequently recognised causes of interstitial lung disease are:

1. Chronic pulmonary oedema, e.g. secondary to mitral valve disease (p. 255).
2. Allergic alveolitis (p. 382).
3. Fibrosing alveolitis associated with the connective tissue disorders or of unknown aetiology (cryptogenic fibrosing alveolitis).
4. Pulmonary damage following therapeutic application of deep X-rays to thorax.
5. Sarcoidosis (p. 409), asbestosis (p. 411), and idiopathic pulmonary haemosiderosis (p. 408).

Although the cardinal features of all forms of interstitial lung disease are similar, these conditions differ considerably in other respects, including aetiology and extrapulmonary manifestations.

Fibrosing Alveolitis

This condition exemplifies many of the typical features of interstitial lung disease. It may be a manifestation of one of the connective tissue disorders, such as rheumatoid disease, systemic lupus erythematosus or systemic sclerosis, or it may occur as an isolated pulmonary abnormality, possibly auto-allergic in origin. Progressive exertional dyspnoea is usually the presenting symptom, often accompanied by a persistent dry cough. In most cases there is gross clubbing of the fingers and toes. Chest expansion is poor, but hyperventilation is always a striking feature. Numerous bilateral coarse crackling crepitations are audible on auscultation. Radiologically, there are diffuse pulmonary opacities, the diaphragm is high and the lungs appear small. The FEV_1 and FVC are reduced proportionately, the gas transfer factor is low, and arterial blood-gas studies show hypoxia and hypocapnia. The diagnosis can usually be made with confidence from these findings, but should in doubtful cases be confirmed by lung biopsy. Serological tests for antinuclear and rheumatoid factors may be positive, even in cases without evidence of connective tissue disorder. The rate of progression of the pulmonary changes varies considerably, from death within a few months to survival with minimal symptoms for many years. Treatment with corticosteroids is effective in perhaps 30 per cent of the acute cases, but not in the others. It may have to be maintained for several years, or even for life.

HONEYCOMB LUNG. The radiological phenomenon of 'honeycomb lung', in which diffuse pulmonary shadowing is interspersed with small, thick-walled cystic translucencies, may be observed in some cases of interstitial lung disease, but it may also be a characteristic feature of certain rare diseases, such as histiocytosis X and tuberous sclerosis. Honeycomb lung, whatever its cause, is associated with an increased incidence of spontaneous pneumothorax, and eventually produces respiratory failure, pulmonary hypertension and right ventricular failure.

Idiopathic Pulmonary Haemosiderosis

This is a rare disease of unknown cause, in which spontaneous haemorrhage into the lungs causes recurrent episodes of pyrexia, haemoptysis and iron-deficiency anaemia. With every incident, red blood cells in large numbers are extravasated into the interstitial tissues of the lungs, where haemosiderin released from macrophages stimulates fibroblastic activity. If the patient survives the acute haemorrhagic episodes, the interstitial fibrosis may eventually cause respiratory failure and pulmonary hypertension.

During the acute episodes widespread coarse crepitations are present, and diffuse stippled shadowing, chiefly involving the mid-zones of both lung fields, is seen on the chest radiograph. In the later stages the clinical and radiographic abnormalities may be indistinguishable from those of fibrosing alveolitis.

PULMONARY FIBROSIS

There are three main types of pulmonary fibrosis:

1. *Replacement fibrosis*, in which the fibrous tissue replaces lung parenchyma damaged by infection or by some other destructive process (e.g. infarction). Fibrosis of this type is a common feature of pulmonary tuberculosis and of all types of pulmonary suppuration (p. 349), and is often associated with bronchiectasis.
2. *Focal fibrosis*, which is a common manifestation of pneumoconiosis (p. 410).
3. *Interstitial fibrosis*, which may be regarded as the end-result of interstitial lung disease (p. 407).

Clinical Features. If pulmonary fibrosis is extensive, it will cause exertional dyspnoea and hypoxia, and this is more likely to be the case in focal and interstitial fibrosis than in replacement fibrosis. On the other hand, the physical signs and radiological changes will usually be more conspicuous in replacement fibrosis, which is generally associated with a gross focal lesion.

Pulmonary fibrosis cannot usefully be discussed as a single entity, and the reader has therefore been referred elsewhere for information on the various causes of this condition.

SARCOIDOSIS

Sarcoidosis is a systemic granulomatous disease of unknown cause. Apart from the absence of caseation and tubercle bacilli, the lesions are histologically similar to tuberculous follicles, but there is no convincing evidence to support the view that the disease is caused by any of the mycobacteria. Chronic beryllium poisoning produces a disease which mimics sarcoidosis both pathologically and clinically, but exposure to beryllium is extremely uncommon and few cases of sarcoidosis can be caused in this way. Histological changes resembling those of sarcoidosis are occasionally seen in individual organs, such as lymph nodes, in conditions such as carcinoma, reticulosis and fungal infections, but these localised 'sarcoid reactions' are not associated with systemic sarcoidosis.

Pathology. The mediastinal and superficial lymph nodes, lungs, liver, spleen, skin, eyes, parotid glands and phalangeal bones are most frequently involved. The characteristic histological feature consists of non-caseating epithelioid follicles. These lesions usually resolve spontaneously but in some cases they stimulate the production of fibrous tissue, which may have grave effects on local structure and function. The disease is seldom fatal, and then only when it affects vital organs such as the lungs, the heart or the central nervous system. An increase in serum calcium, which occurs in rare instances, may produce renal calcinosis and uraemia.

Clinical Features. Sarcoidosis may present in a subacute or a chronic form. Subacute sarcoidosis is usually a benign and self-limiting disorder, spontaneous resolution occurring within two years in most cases. One of its most common manifestations is bilateral and often symmetrical enlargement of the hilar lymph nodes. The paratracheal lymph nodes may also be involved. Erythema nodosum, pyrexia and polyarthralgia may be present at the outset. Later, transient pulmonary changes may be seen on radiological examination in addition to the lymph node enlargement. Other cases of subacute sarcoidosis may present with bilateral parotid swelling or iridocyclitis, which often persist for several weeks. Neurological manifestations, which are uncommon, include arachnoiditis, cranial nerve lesions and polyneuropathy.

Chronic sarcoidosis is a more serious condition, which is less likely to resolve spontaneously and is more liable to cause permanent damage to the structures it involves. Chronic pulmonary sarcoidosis may lead to the development of interstitial fibrosis, pulmonary hypertension and cor pulmonale. The vital capacity and gas transfer factor (p. 320) are the most useful indices of impairment of lung function in this disease. Myocardial sarcoidosis may produce arrhythmias and cardiac failure. The commonest ocular lesion is bilateral chronic iridocyclitis which, if untreated, may cause blindness. Various types of skin lesion may be seen, such as cutaneous 'sarcoids' (reddish-brown papules) or lupus pernio (raised purple plaques, usually on the face, resembling chilblains). Cystic lesions may develop in the phalangeal bones of the hands or feet.

Diagnosis. In most cases skin sensitivity to tuberculin is depressed or absent, and the Mantoux reaction (p. 360) is therefore a useful 'screening' test, a strongly positive reaction to 1 TU virtually excluding sarcoidosis. Although the diagnosis can often be made with a fair measure of confidence from the clinical and radiological features and the tuberculin test, it should, if possible, be confirmed histologically by biopsy of a superficial lymph node or of a skin lesion, when these are present. The Kveim test is also a useful diagnostic procedure, provided a potent antigen can be obtained from human sarcoid tissue. The antigen (0·1 ml) is injected intradermally and when the test is positive a small nodule develops about four weeks later, biopsy of which reveals typical sarcoid follicles.

Treatment. As subacute sarcoidosis usually resolves spontaneously treatment is seldom required, but occasionally, patients with persistent erythema nodosum, pyrexia, parotid swelling or iridocyclitis may have to be given one of the corticosteroid drugs for a short period. Patients with chronic sarcoidosis, particularly if it involves the lungs, eyes or other vital organs, are much more likely to require treatment with corticosteroids, which may have to be continued for several years. The dose should be kept to the minimum required to suppress the manifestations of the disease. Some physicians who believe that sarcoidosis is a form of tuberculosis advise that antituberculosis chemotherapy should be given at the same time, but this is probably unnecessary.

OCCUPATIONAL LUNG DISEASES

In certain occupations the inhalation of dusts, fumes or other noxious substances may give rise to specific pathological changes in the lungs. The nature of each substance, the occupation in which the hazard occurs, the description of each disease, and the pathological changes produced in the lungs are summarised in Table 8.

Diseases Caused by Mineral Dusts (Pneumoconiosis)

The dust particles after inhalation are conveyed by macrophages from the bronchial mucosa to minute foci of lymphoid tissue throughout the lungs. There, the irritation produced by solution of the particles in tissue fluid may initiate widespread pulmonary fibrosis.

The two most common types of pneumoconiosis in Britain are *silicosis* and *coal-worker's pneumoconiosis*. Silicosis, the importance of which was first recognised in Rand gold-miners at the beginning of this century, is caused by the inhalation of dust containing a high proportion of silica particles 3μ or less in size. It occurs in miners who are principally employed in rock-drilling, *Causes and Effects of Occupational Lung Disease*

Cause	Occupation	Description of Disease	Pathological Changes in Lungs
Mineral dusts:			
Coal dust	Coal mining	Coal-workers' pneumoconiosis	Focal and interstitial fibrosis Centrilobular emphysema Progressive massive fibrosis
Silica	Gold mining Iron and steel industries (metal casting) Metal grinding Stone dressing Pottery	Silicosis	
Asbestos	Manufacture of fireproof and insulating materials	Asbestosis	Asbestos bodies Interstitial fibrosis Bronchial carcinoma Pleural mesothelioma
Iron oxide	Arc welding	Siderosis	Mineral deposition only
Tin dioxide	Tin ore mining	Stannosis	
Beryllium	Aircraft and atomic energy industries	Berylliosis	Granulomata Interstitial fibrosis
Organic dusts:			
Cotton, flax or hemp dust	Textile industries	Byssinosis	Acute bronchiolitis Bronchoconstriction
Fungal spores from mouldy hay, straw or grain, mushroom compost, bagasse, etc.	Agriculture and related industries	Farmer's lung Maltworker's lung Mushroom worker's lung Bagassosis	Extrinsic allergic alveolitis
Gases and fumes:			
Irritant gases (ammonia, chlorine, phosgene, sulphur dioxide and trioxide)	Various industries (accidental exposure)		Acute pulmonary oedema
Toluene di-isocyanate	Plastic and rubber industries		Bronchial asthma
Cadmium	Welding and electroplating		Chronic bronchitis and emphysema

and also in foundry workers, metal grinders, stone dressers and pottery workers. It causes a severe, progressive type of fibrosis which in some cases is complicated by tuberculosis. Numerically, however, it is much less important than coal-worker's pneumoconiosis, which is due to the inhalation of coal dust and is particularly prevalent in South Wales. Although the presence of a certain amount of silica in the coal may be a factor in the production of this type of pneumoconiosis, its clinical course differs from that of true silicosis. In a high proportion of cases the condition, although it can be recognised radiologically, is not progressive and causes few if any symptoms. Some cases may, however, as a result of altered immune responses in the damaged lung tissue, proceed to massive fibrosis and death from emphysema and congestive cardiac failure. A few patients may develop pulmonary tuberculosis, with cavity formation and a positive sputum.

Less common types of pneumoconiosis are *asbestosis* and *siderosis*. Asbestosis is due to the inhalation of asbestos fibres, which can be recognised microscopically in the fibrotic areas of lung and as 'asbestos bodies' in the sputum. Siderosis is due to the inhalation of iron oxide and occurs chiefly in electric-arc welders. It seldom causes serious symptoms unless there is co-existent silicosis, as in iron-foundry workers.

It must be emphasised that in most types of pneumoconiosis a long period of exposure to the dust is necessary before radiological changes appear and an even longer period before symptoms arise. Silicosis and coal-worker's pneumoconiosis can seldom be recognised radiologically until there has been at least 10 years' exposure, and in most cases 15 to 25 years' exposure is required.

Clinical Features. Dyspnoea on exertion, which is slowly progressive over a period of 10 to 15 years and which may eventually become severe and incapacitating, is the characteristic symptom of most types of established pneumoconiosis. Cough and sputum due to associated chronic bronchitis are frequently present. The sputum in coal-worker's pneumoconiosis is often black. Clubbing of the fingers may be present in asbestosis. There may be polycythaemia in advanced cases. If pulmonary tuberculosis develops as a complication, additional symptoms such as tiredness, loss of weight, sleep sweats, haemoptysis and pleural pain may occur. Ventilatory failure and right ventricular failure often supervene as terminal events.

Physical Signs in the Chest. In the early stages there are no physical signs directly due to pneumoconiosis, but those of associated chronic bronchitis and emphysema are often present. Even in the later stages the physical signs of pulmonary fibrosis and pulmonary tuberculosis may be obscured by co-existing bronchitis and emphysema.

Radiological Examination. The earliest abnormality is a fine 'nodulation' distributed uniformly throughout both lungs. Later these nodular opacities which at first are small and discrete, resembling the lesions of miliary tuberculosis, become larger and more dense. In coal-worker's pneumoconiosis and silicosis very large opacities due to massive fibrosis may be present. These lesions sometimes break down and form cavities. Cavitation may also occur if tuberculous infection supervenes.

Diagnosis. Pneumoconiosis should be suspected in any person who has chronic respiratory symptoms and has been exposed for many years to dust known to produce the disease. Radiological examination is necessary to confirm the diagnosis and should never be omitted in any suspected case, as pneumoconiosis is a disease scheduled under the National Insurance (Industrial Injuries) Acts. The sputum must always be examined for tubercle bacilli. The degree of disability should be assessed by tests of pulmonary function.

Course and Prognosis. In silicosis and asbestosis the disease pursues a slowly progressive course over 10 to 20 years towards complete invalidism and death from respiratory and cardiac failure. Tuberculosis is a fairly common complication of silicosis but, if adequately treated, it should not worsen the prognosis. In asbestosis, bronchial carcinoma (p. 401) or pleural mesothelioma (p. 417) may cause early death. In cases of coal-worker's pneumoconiosis in which the radiological changes have not progressed beyond the stage of fine nodulation the symptoms may remain mild for an indefinite period, but once progressive massive fibrosis develops the course of the disease differs little from that of silicosis.

Prophylaxis. Pneumoconiosis can be prevented by the wearing of respirators, by damping the dust, and by efficient ventilation systems. These precautions are now compulsory by law in many countries wherever there is a recognised risk of pneumoconiosis.

Treatment. When a diagnosis is made of silicosis or asbestosis, or of coal-worker's pneumoconiosis at the stage of progressive fibrosis, the patient must change his occupation. In cases of coal-worker's pneumoconiosis in which no symptoms are present and the radiological changes have not progressed beyond the stage of 'fine nodulation', work in the pits may be permitted provided that the dust concentration is low and regular clinical and radiological supervision can be undertaken.

In the later stages the treatment is that of chronic bronchitis, ventilatory failure (p. 323) and cardiac failure. If pulmonary tuberculosis supervenes it must be treated with specific chemotherapy (p. 366).

Diseases Caused by Organic Dusts

In *byssinosis* the initial lesion is an acute bronchiolitis, associated with symptoms and signs of generalised airway obstruction which tend to be worse after week-end breaks, but eventually become continuous. There is no radiological abnormality. Recovery usually follows removal from exposure to the dust hazard.

All the other diseases caused by organic dusts are forms of *extrinsic allergic alveolitis*, which have already been fully described (p. 382).

DISEASES OF THE PLEURA

Fibrinous ('Dry') Pleurisy

This term is used to describe cases of pleurisy at the stage of fibrinous exudation when there is no significant degree of effusion. It is usually secondary to bacterial infection in the underlying lung, but may also occur in association with a virus infection (Coxsackie B), which primarily involves the intercostal muscles and is known as '*Bornholm disease*'. Dry pleurisy is a common feature of pulmonary infarction, and may be an early manifestation of pleural invasion by a pulmonary tumour or of pulmonary tuberculosis.

Clinical Features. The characteristic symptom of dry pleurisy is *pleural pain* (p. 321). On examination, rib movement is restricted and the breath sounds, though vesicular, are diminished on the affected side. A *pleural rub* (p. 325) is heard in a high proportion of cases. In all cases the rub is increased by deep breathing and is never heard when the patient is holding his breath except near the pericardium, where a so-called *pleuropericardial rub* may be heard. In the acute stage of dry pleurisy, respiration may be so painful that the limited range of movement of the chest wall may be insufficient to produce an audible rub.

The other clinical features depend on the nature of the lesion causing the pleurisy.

Diagnosis. 'Dry pleurisy' is not a complete diagnosis. An attempt should always be made to find a primary cause. Radiological examination must therefore be performed in every case. A negative radiograph does not necessarily exclude a pulmonary cause for the pleurisy. A preceding history of a few days' cough, purulent sputum and pyrexia is presumptive evidence of a pulmonary infection which may not have been severe enough to produce a radiographic abnormality or which may have resolved before the film was taken.

Dry pleurisy must be distinguished from intercostal myalgia (pleurodynia), fractured rib, costochondritis, herpes zoster, spontaneous pneumothorax and acute upper abdominal disease.

Course. Depending on the cause, complete clinical recovery may ensue or an effusion may develop, either serous or purulent.

Treatment. The primary cause of the pleurisy must be treated. The symptomatic treatment of pleural pain is described on page 334.

Pleural Effusion

This term, by general consent, is applied only to serous effusion. The condition of purulent effusion or empyema is described separately on page 418. The passive transudation of fluid into the pleural cavity (*hydrothorax*) occurs in cardiac failure (p. 246).

The most common causes of pleural effusion are pneumonia, tuberculosis, malignant disease and pulmonary infarction. Pleural effusion, often bilateral, may also be a manifestation of systemic lupus erythematosus (p. 780), rheumatoid disease (p. 770) and reticulosis (p. 753).

Clinical Features. The symptoms and signs of dry pleurisy often precede the development of effusion, but the onset in other cases may be insidious, with little or no pleural pain. Pyrexia occurs in most cases, whatever the primary cause, but is more severe in the presence of infection, and more protracted when the infection is tuberculous.

The principal symptom related to the effusion itself is dyspnoea. The severity of the dyspnoea depends on the size of the effusion and on the rate at which it accumulates.

Physical Signs in the Chest are those of fluid in the pleural space (p. 326).

Radiological Examination shows a dense uniform opacity in the lower and lateral parts of the hemithorax shading off above and medially into the translucency of the lung. When the effusion is loculated, e.g. in an interlobar fissure, a localised opacity is seen.

Diagnosis. The presence of a pleural effusion can usually be recognised from the physical signs, but in some cases it may not be suspected until radiological examination is carried out. Absolute proof that an effusion is present can be obtained only by the aspiration of fluid. A needle should be inserted through an intercostal space over the area of maximum dullness on percussion or, ideally, at the site of maximum radiological opacity as shown by postero-anterior and lateral films or by fluoroscopy. At least 50 ml of fluid should be withdrawn, 20 ml or more being placed in a sterile container for bacteriological examination, 20 ml in a citrated container for cytological examination and 10 ml in a chemically clean container for biochemical examination.

Failure to obtain fluid in a suspected case of pleural effusion is often due to faulty localisation, but if aspiration with a wide-bore needle at various sites is repeatedly unsuccessful, it is unlikely that a significant amount is present. The clinical features and radiological appearances should then be reviewed with four possibilities in mind: pneumonia, pulmonary infarction, pulmonary collapse and pleural thickening.

Pleural thickening, fibrinous or fibrous, which may follow a pleural effusion, produces similar physical signs except that the mediastinum is either central or displaced *towards* the side of the lesion. Thickening of the pleura can often be recognised by a sensation of resistance transmitted from the point of the needle to the hand manipulating the aspirating syringe when the pleura is penetrated.

Many investigations, apart from diagnostic aspiration, may be required to determine the primary cause of a pleural effusion. Estimation of the total and differential leucocyte count in the peripheral blood and examination of the sputum for tubercle bacilli should never be omitted. Radiological examination of the chest may disclose underlying pulmonary disease and indicate its nature. If the lung is obscured by a massive effusion a large volume of fluid should be removed before the film is taken. Pleural biopsy (p. 328) may provide a histological diagnosis in effusions due to tuberculosis or malignant disease. Other investigations which may help to determine the cause of a pleural effusion include bronchoscopy, supraclavicular lymph node biopsy, thoracoscopy and serological tests for antinuclear and rheumatoid factors.

Individual Types of Pleural Effusion

1. TUBERCULOUS PLEURAL EFFUSION

This type of effusion may develop in the course of post-primary pulmonary tuberculosis, but most cases occur in the absence of recognisable pulmonary disease. The pleural infection is always secondary to tuberculosis elsewhere, usually in the underlying lung or in the mediastinal lymph nodes, reaching the pleura by direct extension, by lymphatic spread or, occasionally, by haematogenous dissemination. When a pleural effusion occurs in the absence of radiologically apparent pulmonary tuberculosis it is usually the sequel to a primary tuberculous infection three to six months previously. In these cases, which commonly occur in adolescence or early adult life, and less frequently in childhood, the pleural infection is presumably derived either from a minute subpleural primary pulmonary focus or by lymphatic spread from caseous mediastinal lymph nodes. Although a pleural effusion of this type cannot occur in the absence of tubercle bacilli, the number of bacilli may be small and the disproportionately severe pleural reaction may be due mainly to hypersensitivity of the pleural tissues ('allergy') which develops after the primary tuberculous infection (p. 360).

The onset of a tuberculous pleural effusion may in some cases be sudden, with severe pleural pain preceding the physical signs of effusion for several days. In others the only complaints may be of vague ill-health and loss of weight for a period of weeks or even months before the effusion is discovered. In untreated cases, pyrexia of a remittent type, rising to 39° C. (101-103° F.), is generally present for the first three to six weeks of the illness, and sleep sweats are a common feature. The patient, however, never appears as seriously ill as one with acute pneumonia. There is usually a considerable degree of tachycardia, but the respiration rate is not markedly increased and dyspnoea at rest is present only if the effusion is very large. Unless frank pulmonary tuberculosis co-exists, cough is not a prominent symptom and tubercle bacilli can seldom be isolated from sputum or laryngeal swabs. These tests, however, should be performed in all cases, in conjunction with radiological examination of the chest, to determine whether or not there is an active tuberculous lesion in the lungs.

The total white blood count, which is usually within normal limits in tuberculous pleural effusion, is often a useful diagnostic aid in the early stages of the illness when the differential diagnosis from pneumonia may be difficult.

The pleural fluid in tuberculous effusions is amber or straw-coloured, with a specific gravity of 1·016 or more and a total protein content of over 4 g per 100 ml. It usually clots on standing. The cells, which are relatively few, are chiefly lymphocytes. The fluid is sterile on ordinary methods of culture, but tubercle bacilli can often be isolated on culture or by guinea-pig inoculation. In such cases the sensitivity of the organism to antituberculosis drugs (p. 366) should always be ascertained.

Normal lung fields on radiological examination with negative bacteriological findings in sputum and pleural fluid do *not* exclude tuberculosis as the cause of the effusion, and in young adults a tuberculous aetiology should be assumed unless the tuberculin reaction (p. 360) is negative or some other cause can be clearly established. Now that a simple and effective method of pleural biopsy is available (p. 328) it is possible in many cases to confirm the diagnosis of tuberculous pleurisy histologically and by examining stained sections for acid-fast bacilli.

Treatment. The patient should be kept in bed until the pyrexia has subsided and the pleural fluid has stopped accumulating. Antituberculosis chemotherapy (p. 366) should be started as soon as the diagnosis is made and continued for at least 12 months. If there is an associated tuberculous lesion in the lung, treatment must be maintained for 18 months. As much pleural fluid as can be obtained should be aspirated with a large syringe and needle twice a week until the effusion ceases to reaccumulate. There seems to be no advantage in giving streptomycin intrapleurally in preference to the systemic route.

Very rapid absorption of pleural fluid can usually be obtained by giving a corticosteroid drug such as prednisolone by mouth, in addition to antituberculosis chemotherapy (p. 366).

The patient can be allowed to resume work a few weeks after he starts to get up and provided he takes antituberculosis drugs with complete regularity, no restrictions need be placed on his activities.

2. Post-pneumonic Serous Effusion

A serous pleural effusion may be a complication of any type of pneumonia, but is particularly common with pneumococcal pneumonia. The effusion is usually small and, apart occasionally from a slight recrudescence of pyrexia, seldom produces clinical features distinct from those of the pneumonia itself. In a few cases the effusion becomes purulent: such an outcome was common before the advent of specific treatment.

The pleural fluid is clear, amber or straw-coloured, the cells it contains are predominantly neutrophil leucocytes, and it is usually sterile on culture.

A serous effusion can safely be regarded as 'post-pneumonic', and therefore non-tuberculous, only if there is a preceding history typical of pneumonia, a neutrophil leucocytosis in the blood of over 12,000 per mm^3 and a predominance of these cells in the pleural fluid.

Treatment. Specific treatment for the pneumonia should be continued until after the pyrexia subsides, and the effusion should be aspirated every two or three days until it stops reaccumulating. This usually occurs within 7 to 10 days and if it takes longer the diagnosis should be reviewed, with particular regard to the possibilities of empyema and tuberculous pleural effusion.

3. Malignant Pleural Effusion

The most common cause of pleural effusion over the age of 40 is malignant disease. A malignant effusion is usually secondary to a bronchial carcinoma or to a primary tumour elsewhere. A primary pleural tumour (mesothelioma) may be due to exposure to asbestos (p. 411). Pleural effusion, often bilateral, may occur in patients with reticulosis. A malignant pleural effusion is usually large, and dyspnoea is an early and prominent symptom. Pyrexia may be present but is not as common as with effusions of inflammatory origin.

The pleural fluid may be serous or blood-stained. Clumps of malignant cells may be found by special staining methods.

In some cases bronchoscopy demonstrates a primary bronchial growth. In females the breasts should previously have been examined with care in order to exclude a primary tumour there. When bronchoscopy is negative and the primary tumour is thought to be extrapulmonary, the stomach, kidneys and pelvic organs should be investigated. In most cases, especially if a primary lesion cannot be located, an attempt should be made to obtain histological confirmation of the diagnosis by pleural biopsy (p. 328).

Treatment. Malignant disease of the pleura is incurable, but reaccumulation of fluid, which causes severe dyspnoea and demands frequent pleural aspiration, can often be prevented by treatment aimed at obliterating the pleural space. The method most frequently employed is to inject 20 mg of mustine hydrochloride in 60 ml of normal saline into the effusion, which is then drained by aspiration or through an intercostal tube 24 to 48 hours later. By this time the visceral and parietal surfaces are acutely inflamed, and tend to adhere when the lung re-expands. Although mustine, a cytotoxic drug, may produce some necrosis of tumour cells on the pleural surfaces it is of value in the treatment of malignant pleural effusion chiefly or entirely because it is a chemical irritant, and other substances with similar properties (p. 425) may be equally effective.

4. Pulmonary Infarction

This is a common cause of a small effusion, which may be blood-stained and which often contains large numbers of eosinophil leucocytes. The diagnosis can usually be made from the other clinical and radiological manifestations.

Treatment. This is described on page 284.

Empyema Thoracis

This is the term used to describe the presence of pus in the pleural space. The pus may be as thin as serous fluid, or so thick that it is difficult to aspirate through even a wide-bore needle. Microscopically, neutrophil leucocytes are present in large numbers. The causative organism may or may not be isolated from the pus. An empyema may involve the whole pleural space ('total' empyema) or only part of it ('loculated' or 'encysted' empyema). It is almost invariably unilateral.

Aetiology. Empyema is always secondary to infection in a neighbouring structure, usually the lung. The principal pulmonary infections liable to produce empyema are the specific and suppurative pneumonias, and tuberculosis. Extrapulmonary causes of empyema are less common, but this condition may follow an infected penetrating wound of the chest wall. A haemothorax may become infected or a subphrenic abscess may rupture through the diaphragm. Empyema has become a relatively rare disease because pulmonary infection can now be so readily controlled.

Pathology. Both layers of pleura are covered with a thick, shaggy, inflammatory exudate. In the course of time the exudate becomes converted into fibrous tissue which may encase the collapsed lung so rigidly that it cannot re-expand when the pus is removed by aspiration or by an external drainage operation. The pus in the pleural space is often under considerable pressure and if the condition is not adequately treated it may rupture into a bronchus, from which it is expectorated, or through an intercostal space with the formation of a subcutaneous abscess or sinus. When an empyema ruptures into a bronchus, a bronchopleural fistula is produced. This allows air to enter the pleural space, and a pyopneumothorax is formed.

The only way in which an empyema can heal is by apposition of the visceral and parietal layers of the pleura with obliteration of the empyema space by organisation of the intervening exudate. This cannot occur unless re-expansion of the collapsed lung is secured *at an early stage* by removal of all the pus from the pleural space. Re-expansion of the lung cannot take place if, through delay in treatment or inadequate drainage, the visceral pleura becomes grossly thickened and rigid, if the pleural layers are kept apart by air entering the pleura through a bronchopleural fistula, or if disease in the lung itself, such as bronchiectasis, bronchial carcinoma or pulmonary tuberculosis, renders it incapable of re-expansion. In all these circumstances an empyema tends to become chronic and healing may not take place without recourse to major thoracic surgery.

Clinical Features. Empyema should be suspected in patients with pulmonary infection if there is a recurrence of pyrexia which fails to respond or responds only partially to the continued administration of a suitable antibiotic. In other cases the illness produced by the primary infective lesion may be so slight that it passes unrecognised and the first definite clinical features are due to the empyema itself.

In the fully developed case two separate groups of clinical features are found:

1. THOSE DUE TO ABSORPTION OF TOXINS FROM UNDRAINED PUS:

(*a*) Pyrexia, usually high and remittent but sometimes slight.
(*b*) Rigors, sweating, malaise, anorexia and loss of weight.
(*c*) Neutrophil leucocytosis in the blood.

2. THOSE DUE TO THE LOCAL EFFECTS OF THE EMPYEMA:

(*a*) *Dyspnoea*, when the empyema is large.
(*b*) *Pleural pain*, usually confined to the initial stage of the illness.
(*c*) *Cough and purulent sputum*, usually related to the primary lung disease, but occasionally caused by the rupture of an empyema into a bronchus.

Physical Signs in the Chest. An empyema usually produces the typical signs of fluid in the pleural space (p. 326), but occasionally, as with a serous effusion, the breath sounds may be bronchial instead of diminished or absent. In these cases, however, the presence of fluid can usually be suspected from the 'stony' dullness of the percussion note.

A small localised empyema, particularly when situated in an interlobar fissure, may produce no abnormal physical signs.

Radiological Examination. The appearances are indistinguishable from those of serous pleural effusion (p. 415). When air is present in addition to pus (pyopneumothorax), a horizontal 'fluid level' marks the junction of the fluid and the air if the film is taken in the erect position.

Diagnosis. Although the clinical features suggest the diagnosis in most cases, final confirmation of the presence of an empyema depends on the aspiration of pus. A wide-bore needle should be inserted through an intercostal space over the area of maximal dullness on percussion. Whenever possible the position of the empyema should have previously been confirmed by postero-anterior and lateral radiographs. Bacteriological examination of the pus may help to determine the cause of the empyema.

In post-pneumonic cases where intensive treatment with antibiotics has been given the pus is frequently sterile. The distinction between tuberculous and non-tuberculous cases can usually be made from the radiological changes in the lungs or by the isolation of tubercle bacilli from pus or sputum.

Course and Prognosis. If an acute empyema is unrecognised or inadequately treated the patient may die as a result of toxic absorption from the undrained pus. Alternatively, the empyema may pass on to the chronic stage and cause general ill-health, recurrent episodes of pyrexia, clubbing of the fingers and sometimes amyloid disease. A non-tuberculous empyema, treated early, usually heals quickly; one which is drained at a late stage seldom heals without further surgical intervention. Tuberculous empyema is potentially a serious condition, difficult to treat and slow to heal.

Treatment

NON-TUBERCULOUS EMPYEMA

1. *Acute.* When the patient is acutely ill, and the pus is thin in consistence:

(*a*) An intercostal tube should be inserted into the most dependent part of the pleural space and connected to a water seal drainage system (p. 424).

(*b*) An antibiotic to which the organism causing the empyema is sensitive should be given by intramuscular injection or by mouth.

If treatment is started early enough, and the organisms are drug-sensitive, an empyema can often be aborted by these measures. If, however, the intercostal tube is not providing adequate drainage, which is apt to happen when the pus thickens and clots, a short segment of rib should be resected, the empyema cavity cleared of pus and clot, and a wide-bore open drain inserted.

2. *Chronic.* If a diagnosis is made before any drainage procedure is carried out, it may be feasible to resect the empyema sac *in toto*, provided the patient is fairly fit and the underlying lung is healthy. If open drainage has been performed, and re-expansion of the lung is prevented by gross thickening of the visceral pleura, 'decortication' may be required. This procedure will allow the lung to re-expand and obliterate the pleural space. Few patients nowadays need to be left with a permanent pleural drain, but this may be unavoidable when respiratory function is poor, or if the underlying lung is badly damaged and the patient is unfit for a major pulmonary resection.

TUBERCULOUS EMPYEMA. The empyema should be drained, as for non-tuberculous infection, and antituberculosis chemotherapy (p. 366) should be started immediately. In many cases treated in this way the drainage tube can be removed when the infection has been controlled, but occasionally surgical measures are required to ablate the residual space.

Spontaneous Pneumothorax

Aetiology. The two chief causes of spontaneous pneumothorax are:

1. Rupture of a subpleural emphysematous bulla or of the pulmonary end of a pleural adhesion.
2. Rupture of a subpleural tuberculous focus into the pleural space.

In Britain the first cause is very much more common than the second. Active pulmonary tuberculosis is, in fact, responsible for very few cases of spontaneous pneumothorax, a finding which is in sharp contrast with the experience of 50 years ago.

Certain other conditions such as staphylococcal lung abscess, pulmonary infarction and bronchial carcinoma may, in rare instances, give rise to spontaneous pneumothorax. As with tuberculosis, the pneumothorax in all these conditions results from the rupture of a pulmonary lesion situated close to the pleural surface.

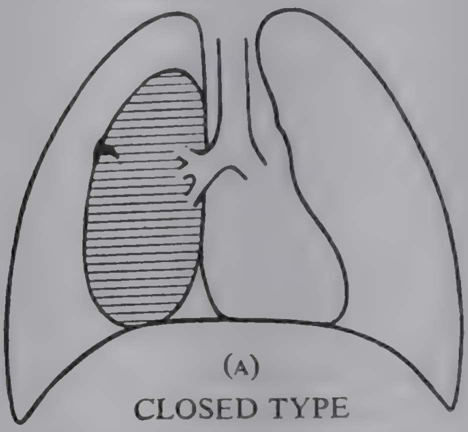
Pathology. There are three types of spontaneous pneumothorax:

1. *Closed* (Fig. 60A). The communication between pleura and lung seals off as the lung collapses, and does not re-open. In this type of case the air is gradually absorbed and the lung re-expands.

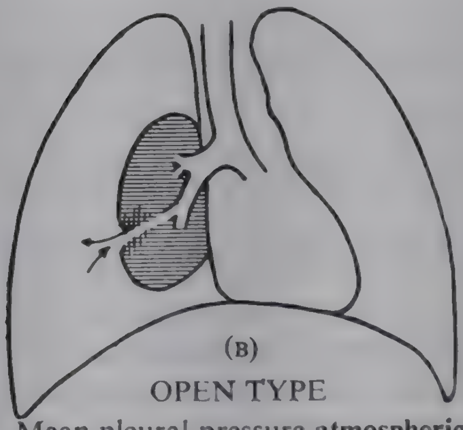
2. *Open* (Fig. 60B). The communication is generally with a bronchus ('broncho-pleural fistula') and does not seal off when the lung collapses. The air pressure in the pleural space thus approximates to atmospheric pressure throughout both inspiration and expiration and the lung cannot re-expand. Moreover, the large bronchial communication facilitates the transmission of infection from the air passages into the pleural space and empyema is a common complication.

3. *Valvular* (Fig. 60C). The communication between pleura and lung persists but is small and acts as a one-way valve which allows air to enter the pleura during inspiration but prevents it from escaping during expiration. Very large

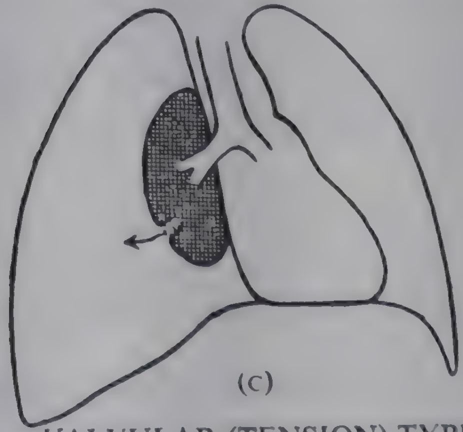
amounts of air may be 'trapped' in the pleural space during bouts of coughing and the intrapleural pressure may rise to well above atmospheric level. This results not only in complete collapse of the underlying lung but also in gross mediastinal displacement towards the opposite side with compression of the opposite lung. This type of pneumothorax is usually referred to as a 'tension pneumothorax'.



(A)
CLOSED TYPE
Mean pleural pressure negative



(B)
OPEN TYPE
Mean pleural pressure atmospheric



(C)
VALVULAR (TENSION) TYPE
Mean pleural pressure positive

FIG. 60
THE MECHANISMS OF SPONTANEOUS PNEUMOTHORAX

Clinical Features. The onset is usually sudden, with pain or a feeling of 'tightness' on the affected side of the chest, which may be aggravated by deep inspiration.

The patient then becomes increasingly breathless and in severe cases cyanosis appears, sometimes of a marked degree. The physical signs in the chest are those of air in the pleural space (p. 326). When the pneumothorax is small and localised there may be no abnormal signs, and the condition may be revealed only by radiological examination.

With the *closed* type of spontaneous pneumothorax the dyspnoea, which is seldom severe, gradually abates over the course of a few days. Progressive spontaneous absorption of the air takes place and re-expansion of the lung is complete between two and six weeks later, depending on the initial size of the pneumothorax. Pleural infection is uncommon in this type of pneumothorax.

The *open* type of spontaneous pneumothorax is usually of tuberculous origin. The onset is similar to that of the closed type, but the dyspnoea, although it is not rapidly progressive, does not improve and within a few days the appearance of pyrexia and systemic disturbance, accompanied by physical and radiological signs of air and fluid in the pleural space, indicate the development of a pyopneumothorax. In tuberculous cases acid-fast bacilli can be isolated from the pleural fluid at an early stage.

The *valvular* type of pneumothorax ('tension pneumothorax') produces the most dramatic clinical picture of all. The dyspnoea is rapidly progressive from the start and is accompanied by central cyanosis. The patient may die from asphyxia within a few minutes, but usually the course of events is less rapid and medical attention can be obtained in time to avert a fatal outcome.

Recurrent spontaneous pneumothorax is not uncommon, especially in patients with emphysematous bullae. Subsequent incidents usually occur on the same side as the first but may also occur on the opposite side.

Radiological Examination shows the sharp edge of the collapsed lung, and between this and the chest wall there is complete translucency with no lung markings. The degree of pulmonary collapse varies from case to case.

Diagnosis. The diagnosis of spontaneous pneumothorax can usually be made on the history and physical signs but should, whenever possible, be confirmed by radiological examination. This also shows the size of the pneumothorax and the degree of mediastinal displacement, and gives information regarding the presence or absence of pleural fluid and underlying pulmonary tuberculosis. Bacteriological examination of sputum and of pleural fluid, if present, is of great importance in distinguishing tuberculous from non-tuberculous cases.

Treatment

1. *Closed Spontaneous Pneumothorax.* When the pneumothorax is small and the patient is only slightly dyspnoeic no treatment is required but observation should be continued until re-expansion of the lung is complete. If, however, the pneumothorax is large and causing moderate or severe dyspnoea, it is

essential to employ more active measures. Immediate and complete re-expansion of the lung can be obtained by inserting a catheter into the pleural cavity through an intercostal space and connecting it to a water-seal drainage system (Fig. 61). The catheter is left in place for five or six days. This form of treatment considerably shortens the period of incapacity.

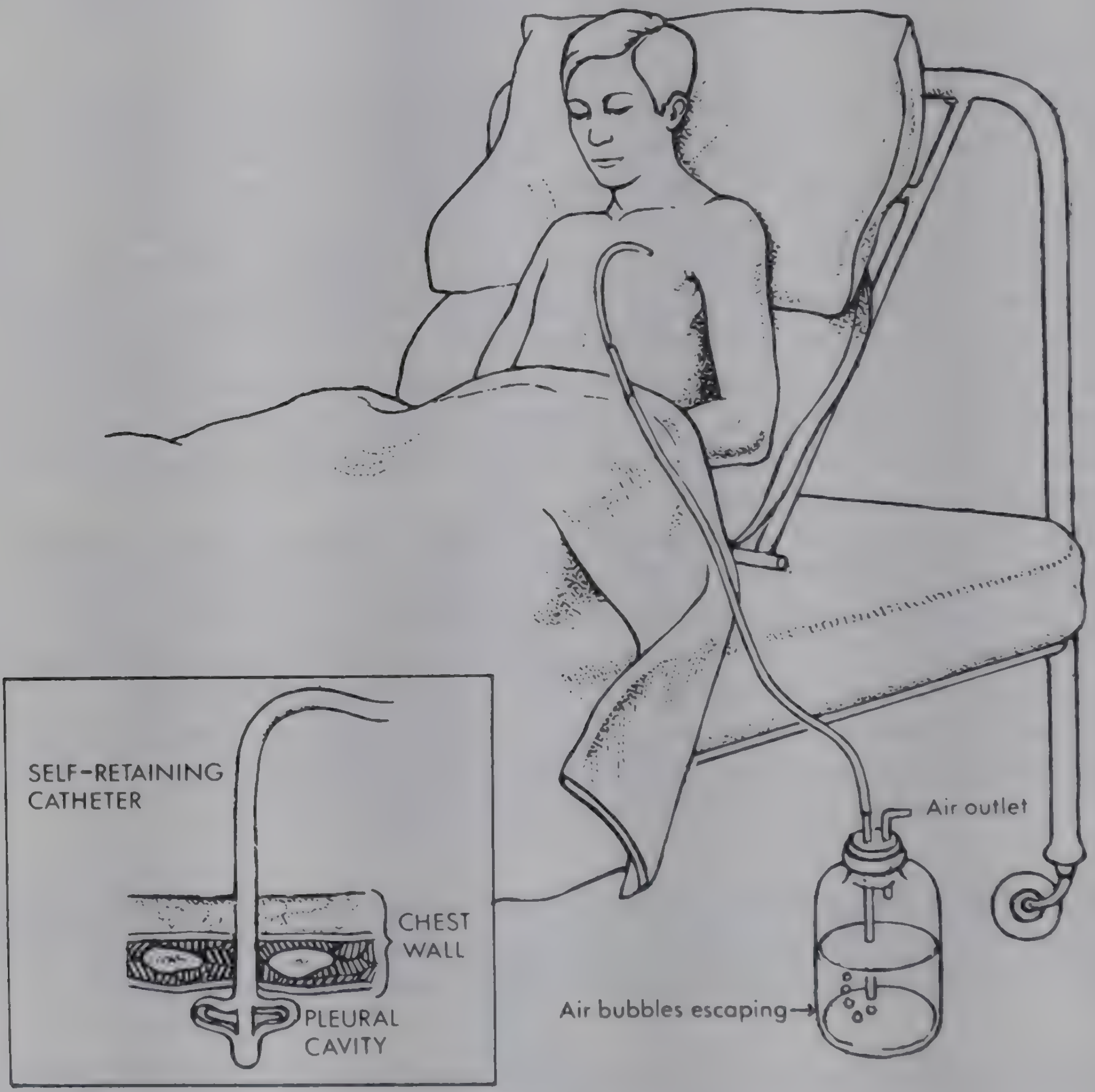


FIG. 61

TREATMENT OF SPONTANEOUS PNEUMOTHORAX BY PLEURAL INTUBATION AND 'WATER-SEAL' DECOMPRESSION

The water-seal allows air to leave the pleural space but prevents it from re-entering. This reduces the intrapleural pressure and promotes re-expansion of the lung. The insert shows the position of the self-retaining (Malecot) catheter in the pleural space.

If a tuberculous aetiology is suspected, specific chemotherapy (p. 366) should be started immediately. If a pleural effusion develops, the fluid may be drained through the catheter by suitable posturing or aspirated with a needle and syringe.

2. *Open Spontaneous Pneumothorax*. There is a frank bronchopleural fistula, and pleural infection rapidly supervenes. Such cases are seldom amenable to

medical treatment and, whether tuberculous or non-tuberculous, should be referred to a thoracic surgeon for treatment of the resulting pyopneumothorax.

3. *Tension Pneumothorax*. This constitutes an acute medical emergency. An intercostal catheter should be inserted at once and connected to a water-seal drainage system, as shown in Figure 61. Symptomatic relief is immediate and dramatic. If suitable equipment for this procedure is not at hand a wide-bore needle should be used instead. This should be attached to a length of tubing, the end of which should be placed under water in a bottle or basin.

4. *Recurrent spontaneous pneumothorax*, unilateral or bilateral, is first treated by the introduction of an irritant substance, such as an emulsion of kaolin, into the pleural space. This procedure (artificial pleurodesis) produces an aseptic pleurisy, which results in the formation of extensive adhesions between the parietal and visceral surfaces, and usually prevents further episodes of spontaneous pneumothorax. Parietal pleurectomy is a more reliable method of artificial pleurodesis, but involves a major thoracic operation.

DEFORMITIES OF THE CHEST WALL

An increase in the antero-posterior diameter of the chest relative to the lateral diameter is a common feature of emphysema, but only the most severe forms of this abnormality merit the description of 'barrel chest'. *Pectus carinatum* ('pigeon chest') is seen in patients who have suffered from severe obstructive airway disease (chronic bronchitis or asthma) since early childhood. *Pectus excavatum* ('funnel chest') is a condition in which the body of the sternum, often only its lower end, is curved backwards. The heart is displaced to the left, and may be compressed between the sternum and vertebral column, but only very rarely is this associated with disturbance of cardiac function. It may, however, restrict chest expansion and reduce the vital capacity. The impairment of cardiac or pulmonary function is seldom sufficiently severe to warrant surgical correction, but this may be indicated for cosmetic reasons.

Severe *thoracic kyphoscoliosis* causes ventilation: perfusion imbalance in the lungs and pulmonary underventilation. Many patients with this type of chest deformity later develop ventilatory failure, pulmonary hypertension and right ventricular failure, and most of them die before the age of 50. The tempo of deterioration is often accelerated by bacterial infection in the bronchi and lungs. The prognosis in these cases can be improved only by early surgical correction of the spinal deformity. Ventilatory failure may also occur in ankylosing spondylitis, particularly if there is any interference with the function of the diaphragm.

PREVENTION OF RESPIRATORY DISEASE

The main causes of respiratory disease are: infection, mechanical derangements of the bronchi, lungs or pleura, allergic phenomena, occupational dust hazards, tobacco smoking and atmospheric pollution.

The preventive measures applicable to each cause will be discussed in turn.

Infection

The following are the most important factors in the prevention of respiratory infection:

1. *The avoidance of contact with persons suffering from a specific respiratory infection.* The strict application of this principle may be unnecessary in diseases of low infectivity such as pneumococcal pneumonia or impracticable in the case of ubiquitous diseases such as coryza or influenza. It has its most important application in the infectious 'fevers', such as measles and whooping-cough, and in tuberculosis, particularly when the subject at risk is a child. In all infective diseases, however, the improvement of housing conditions with the eradication of overcrowding must be regarded as an essential preventive measure. Improved ventilation of public transport vehicles, factories, shops and places of entertainment would also help to limit the spread of respiratory infection.

The wearing of face masks by persons suffering from acute upper respiratory infections in order to prevent dissemination of disease is hardly feasible in ordinary circumstances, but this precaution should always be taken by members of the medical, nursing and domestic staff of hospitals, especially children's hospitals, if they have to remain on duty while suffering from such an infection.

2. *Natural and acquired immunity to infection.* Natural immunity, although of importance in determining the outcome of an exposure to infection, has little practical bearing on the prevention of respiratory infection, except possibly in the case of tuberculosis (p. 370). The artificial production of acquired immunity is, however, of considerable value in the prevention of tuberculosis (p. 371) and of diseases such as diphtheria, whooping-cough, influenza and measles, which are liable to have serious respiratory complications. The use of vaccines prepared from autogenous pyogenic bacteria for the prevention of coryza and bronchitis is now considered to be of no value.

3. *Curbing the misuse of antibiotics.* If antibiotics are given indiscriminately to patients with advanced chronic bronchitis and bronchiectasis, antibiotic-resistant bacteria such as *Staph. pyogenes* and Gram-negative bacilli, and fungi such as *A. fumigatus*, will come to dominate the respiratory tract flora. This may endanger not only the patient himself but also any persons suffering from chronic bronchopulmonary disease with whom he may come into contact, e.g. in a hospital ward.

Mechanical Derangements of the Bronchi, Lungs and Pleura

Suitable pre-operative measures can do much to prevent bronchial obstruction by tenacious secretion, which is liable to complicate thoracic and abdominal operations (p. 400). The proper supervision of children reduces the risks of the accidental inhalation of a foreign body, and adequate protection of the larynx during operations on the mouth and throat under general anaesthesia will virtually eliminate the possibility of the inhalation of teeth, tissue fragments or blood clot. Bronchiectasis can to a large extent be prevented by the early and adequate treatment of pulmonary infection and by the prompt relief of bronchial obstruction, where that is possible.

As the cause of emphysema is not known, no measure is available to prevent it, but encouragement to stop smoking and the prophylaxis and early treatment of bronchial and pulmonary infection can undoubtedly mitigate the effects of this disease and of chronic bronchitis. Pulmonary fibrosis occurring as a sequel to pulmonary infection may be prevented by the early and adequate control of such infection.

There are no known means of preventing the initial episode of spontaneous pneumothorax, but the risks of a recurrence can be eliminated by the induction of an artificial pleurisy to obliterate the pleural space.

Allergic Phenomena. Hay fever can in some cases be prevented by the routine use of an antihistamine drug during the pollen season or by pre-seasonal desensitisation with the causal antigen. The complex problems involved in the prevention of bronchial asthma have been discussed on page 380.

Occupational Dust Hazards. Adequate ventilation of industrial and agricultural premises, measures to reduce airborne dust in coal mines and steel foundries, and the compulsory wearing of face masks where necessary, can prevent diseases such as coal-worker's pneumoconiosis, silicosis, asbestosis and farmer's lung.

Tobacco Smoking and Atmospheric Pollution. It has now been firmly established that the smoking of tobacco (especially cigarettes) is the principal factor in the production of bronchial carcinoma and chronic bronchitis. The polluted atmosphere of industrial cities and towns also contributes to the high incidence of these diseases. Both are thus preventable and it is the duty of the medical profession actively to discourage the habit of smoking and to support vigorously the drive for 'clean air'.

I. W. B. GRANT.
N. W. HORNE.
G. J. R. MCHARDY.

Further reading:

Bates, D. V. Macklem, P. T. & Christie, R. V. (1971). *Respiratory Function in Disease*. Philadelphia: Saunders.

Cotes, J. E. (1968). *Lung Function: Assessment and Application in Medicine*. Oxford and Edinburgh: Blackwell Scientific Publications.

Crofton, J. & Douglas, A. C. (1969). *Respiratory Diseases*. Oxford and Edinburgh: Blackwell Scientific Publications.

Grant, I. W. B. (1973). Examination of the respiratory system. In *Clinical Examination*, 3rd ed., edited by Macleod, J. Edinburgh and London: Churchill Livingstone.

Ross, J. D. & Horne, N. W. (1969). *Modern Drug Treatment in Tuberculosis*. London: Health Horizon Limited.

Scottish Home and Health Department and Scottish Health Services Council (1969). *Uses and Dangers of Oxygen Therapy*. Edinburgh: Her Majesty's Stationery Office.

Diseases of the Digestive System

FUNCTIONS OF THE GASTROINTESTINAL TRACT

THE gastrointestinal tract is a coordinated structure with the function of ingesting and absorbing nutrients and excreting unabsorbed and waste products. It should not be regarded as a series of separate organs since the role of each component is closely related to that of other parts of the tract. Its functions may be subdivided into:

(1) **Controlling and Coordinating Mechanisms.** The autonomic nervous system and hormones, including gastrin, secretin and pancreozymin-cholecystokinin, control and coordinate motility and secretion.

(2) **Motility.** The carefully controlled motility of the tract is responsible for the orderly progression of nutrients through the system so that the stage of digestion and absorption is appropriate to a given region of the tract.

(3) **Secretion.** The secretion of enzymes and detergents enables protein, carbohydrate and fat to be digested prior to absorption. The secretion of electrolytes provides the correct pH for each stage of digestion.

(4) **Absorption.** The absorptive system consists of specialised cells, together with a portal venous system and lymphatics.

(5) **Defence Mechanisms.** These are necessary to protect the mucosa from its own digestive enzymes and from the bacterial population to which it is exposed. These mechanisms include a rapid turnover of the epithelial cells, the production of mucus and a specialised immunological system.

1. The Controlling and Coordinating Mechanisms

The smooth muscle and the secretory cells of the gastrointestinal tract are richly supplied by the autonomic nervous system. Pre-ganglionic parasympathetic fibres of the vagi synapse with the parasympathetic motor neurons of the enteric plexuses. Sympathetic fibres run in the vagal and the splanchnic nerves to make contact with the plexuses and the smooth muscle cells. The plexuses are situated at different levels in the bowel wall—subserous, myenteric, submucosal and mucosal—each varying in density from organ to organ. In general, the parasympathetic system is excitatory and the sympathetic inhibitory but there is also evidence for nonadrenergic inhibitory nerves. This nervous system exerts an effect on the contraction of the smooth muscle cells and on the secretion of enzymes, electrolytes and hormones by the mucosa. It is assisted in its control by sensory nerves in the mucosa and in the gut wall which respond to chemical stimuli and to stretch, and by the enteric hormones. Since these are released in response to food in the upper gastrointestinal tract, it is logical that they should modify nervous control so as to affect the progression of nutrients as well as being the prime agent for the stimulation of secretions. The hormone gastrin is released from the antral mucosa in response to vagal stimulation, mechanical stimulation and contact with ingested protein; it then stimulates the body of the stomach to produce acid and pepsin to digest the protein. As with the stomach, exocrine pancreatic secretion is stimulated partly through nervous and partly through hormonal mechanisms. The nervous mechanisms operate through the vagus, and prime the acinar cells to secrete in response to the hormones secretin and pancreozymin which are liberated when the gastric chyme comes into contact with the mucosal cells of the duodenum. Secretin and pancreozymin-cholecystokinin are released from the duodenal mucosa in response to acid, fat and hypertonic solutions. Secretin stimulates the secretion of bicarbonate by the pancreas and biliary tract epithelium whereas pancreozymin-cholecystokinin stimulates contraction of the gall-bladder and the secretion of enzymes by the pancreas. It is probable that pancreozymin and cholecystokinin are one and the same hormone.

2. Motility

Apart from the striated muscle in the upper oesophagus, smooth muscle is responsible for the motility of the gastrointestinal tract. The smooth muscle has myogenic activity and produces ‘slow waves’ which are spontaneous, slow depolarisations conducted over long distances because of the close contact between cells. These do not result in contraction but they enable contractions in different areas to be coordinated. At a certain point in the slow wave ‘action spikes’ can occur which initiate contraction of the muscle.

Oesophagus. The upper oesophageal sphincter is formed largely by the striated cricopharyngeus muscle which exerts constant tone to keep the sphincter closed except during swallowing. Once the upper oesophageal sphincter relaxes, peristalsis sweeps along the length of the body of the oesophagus, but occasionally, even in the normal oesophagus, the contractions are not coordinated correctly. In the disorder of diffuse spasm these uncoordinated contractions predominate. The lowest few centimetres of the oesophagus form the lower oesophageal sphincter. This has a high resting tension which prevents reflux of gastric contents into the oesophagus. Normally the sphincter relaxes when the peristaltic wave arrives but the characteristic feature in achalasia is that it fails to do so. The sphincter is controlled by nervous and hormonal mechanisms. It is supplied by the sympathetic and parasympathetic systems both of which may cause contraction. The high serum concentration of gastrin after a meal also increases tension in the sphincter at a time when the sphincter is subject to the stress of a full stomach.

Stomach. When the swallowed food arrives in the stomach, receptive relaxation occurs so that a large increase in volume is accompanied by only a small rise in pressure within the lumen. The gastric slow wave controls the frequency and direction of antral peristalsis which is responsible for the thorough mixing of the gastric contents and their progressive emptying into the duodenum. Several mechanisms exist to prevent the duodenum receiving more nutrient than it can deal with. Chemoreceptors for fat and acid and osmoreceptors in the duodenal mucosa control gastric emptying by means of local reflexes and by regulating the secretion of secretin and pancreozymin. Approximately half of a semisolid meal has left the stomach in about 30 minutes.

Small Intestine. Again, coordination is due to the slow wave in the longitudinal muscle fibres. It is the pacemaker which dictates the times at which any given segment of the gut can contract. The frequency of the slow wave in the duodenum is greater than in the ileum, thus enabling the proximal bowel to override more distal areas. By this means contractions are coordinated both to mix and propel the small bowel content so that all nutrients can be exposed to the absorptive cells. It is thought that the myenteric plexus and the enteric hormones determine the local response to the slow wave so that contraction may or may not occur depending on the state of affairs in the lumen at any one time.

Colon. Motility here is poorly understood. There is probably a slow wave but it is not known how it coordinates contractions. Observation of the colon suggests two main types of contraction occur which may be associated with two different functions. Firstly, there is segmentation which consists of contraction rings forming and disappearing over long periods of time: these produce a slow mixing of faeces but no propulsion, thus facilitating the absorption of water and electrolytes. Secondly, propulsion occurs through 'mass movement', a peristaltic wave which occurs several times a day. This action carries out the second function of the colon, namely the elimination of faeces. All activity in the colon is increased after eating, and defaecation is more likely to occur at this time. The enteric hormones may be responsible for this activity. Finally, in diarrhoea the colon is quiet whereas in constipation colonic activity is greater than normal. This is explained on the basis that the main activity in the colon, segmentation, causes mixing only and is responsible for the resistance to flow along the lumen.

3. Secretion

The production of secretions for the digestion of nutrients is under nervous and hormonal control.

Gastric Secretion. The vagus stimulates acid and pepsin secretion in response to the sight or smell of food by a direct effect on the parietal and peptic cells. This is known as the cephalic phase of gastric secretion. It also initiates the release of gastrin from the antrum. Sustained acid and pepsin secretion occurs as a result of the prolonged release of gastrin due to the presence of protein and amino acids in the antrum of the stomach. Histamine is also an effective stimulant of acid secretion and it is thought that gastrin may stimulate acid secretion through the release of histamine as a mediator. The primary secretion of the parietal cell is thought to be isotonic with blood and a concentration of acid of 150 mEq/*l* can be present in gastric aspirates. Mechanisms are required to turn off gastric secretion once digestion within the stomach is complete. These mechanisms are largely the same ones which slow gastric emptying, i.e.

the release of the enteric hormones secretin and pancreozymin-cholecystokinin and also the presence of a low pH in the gastric antrum which inhibits the further release of gastrin.

Pancreatic Secretion, Bile and Intestinal Secretions. These secretions are released into the lumen of the intestine in response to nutrients in the duodenum and upper small intestine. Bicarbonate is secreted by the pancreas and the biliary tract epithelium in response to secretin. The bicarbonate neutralises gastric acid and provides a neutral pH for the activity of pancreatic enzymes and the formation of micelles (p. 488). The pancreatic enzymes lipase, amylase and trypsin are produced in response to pancreozymin-cholecystokinin which also causes contraction of the gall-bladder so that an adequate supply of bile salts reaches the intestine at a time when fat has to be digested. The importance of these events is discussed further under malabsorption (p. 488). The enteric hormones are also responsible for the secretion, by the mucosa of the small intestine, of succus entericus which contains bicarbonate and additional enzymes.

4. The Absorptive System

To increase the surface area for absorption in the small intestine the mucosa is formed into villi and the surface of the absorptive cells is specialised in the form of microvilli. The microvilli possess a multitude of enzyme systems for the final stages of digestion of nutrients followed by their absorption. In coeliac disease the surface area of the small intestine is reduced because of the absence of villi and malabsorption results.

Under normal circumstances nutrients are transported from the absorptive cell by the lymphatic system (for example fat and fat soluble vitamins) or by the portal venous system (amino acids and hexoses). The absorptive system is discussed in more detail on page 488.

5. Defence Mechanisms

Cell Turnover. The epithelial cells of the gastrointestinal tract are constantly renewed so that, for example, the epithelial surface of the small intestine is replaced every 48 hours. The desquamated cells are digested and their products reabsorbed. In the intestine, cellular turnover has been shown to be slower than normal in germ-free animals and it can be argued that this turnover is to some extent a protective mechanism. Drugs which slow down cell turnover tend to predispose to peptic ulceration in the stomach and duodenum.

Production of Mucus. Mucus producing cells are present at all levels of the gastrointestinal tract. Mucus may provide a protective covering for the mucosa and when its composition is altered, for example by corticosteroids, peptic ulceration may occur.

Immunological System. The lamina propria of the stomach and intestines contains many lymphocytes and plasma cells. Some of these cells synthesise secretory IgA (p. 24) which is resistant to digestion by intestinal enzymes and probably plays a role in protecting mucosal surfaces from bacterial invasion. It is thus of particular importance in the small intestine where bacterial colonisation is deleterious.

THE SYMPTOMS OF GASTROINTESTINAL DISEASE

Disease of the gastrointestinal tract may produce sensations which the patient finds difficulty in describing or localising. Thus the feeling that 'something is wrong' becomes couched in indefinite terms as 'wind', 'indigestion', 'flatulence', etc. It is important to define such symptoms as accurately as possible since each may indicate the presence of disease in a particular part of the gastrointestinal tract.

Pain

This is often the most important symptom of gastrointestinal disease and there are several possible mechanisms for its occurrence.

1. Strong or disordered contractions of the smooth muscle due to obstruction or distension of the viscus or inflammation of the mucosa. This type of pain is likely to wax and wane over a few minutes and is often referred to the surface of the body at a site away from the disordered viscus.
2. Inflammation of the visceral and parietal peritoneum. Here the pain is constant and more related to the site of its origin.
3. Stretching of the capsule of a viscus, for example, the liver or spleen.

Reference of Pain. Pain may be referred to the abdominal wall, the chest or back. Oesophageal pain may be felt in the chest or back. It can be localised over the site of the lesion but lesions at the lower end of the oesophagus may give pain at the suprasternal notch. Pain from foregut structures, stomach, duodenum, gall-bladder and pancreas, is referred to the epigastrium but pain from the duodenum and pancreas is often referred to the back between the eighth and tenth thoracic vertebrae. Pain from midgut structures, the jejunum and ileum, is referred to the mid abdomen but there may be pain in the back between L1 and L3. The colon and rectum tend to refer to the hypogastrium. In all cases the pain is central and across the abdomen and not unilateral. Pain in the lower part of the rectum due to disordered motility is termed tenesmus and it produces an unproductive and intense desire to empty the bowel.

Relationship to Physiological Activities. In the patient with pain it is important to determine the time of occurrence. Pain which regularly awakens the individual is usually due to a duodenal ulcer as is pain relieved by food. Pain relieved by a bowel movement is likely to originate in the colon.

Severity and Duration of Pain. Some forms of pain, for example, biliary pain ('colic') are almost unbearable, whilst others may amount only to mild discomfort. Biliary 'colic' often lasts for 6 to 10 hours and the pain of acute pancreatitis may be even longer. Pain which is not particularly severe but which is said to last all day is usually an expression of a psychological disturbance.

Quality of Pain. This is the least reliable indication of the cause of the pain because the patient cannot describe it. Whatever the description, it is the location of the pain and its relationship to other events which may provide the diagnosis. However the more bizarre the description of the pain, the less likely it is to be of organic origin.

Change in Hunger, Appetite, Food Habits or Weight

These may be mentioned by the patient but if not, enquiry about them should be made by the physician. In health most individuals maintain a steady weight and this is facilitated, in part, by sensations arising in the upper gastrointestinal tract.

Hunger. This is described as an often unpleasant sensation partly localised to the epigastrium. In addition, there may be weakness, irritability and headache. The mechanism of the hunger sensation is unknown. It has been postulated that it is due to vigorous contractions of the stomach but similar contractions after food do not cause hunger and furthermore the patient may still experience hunger after a subtotal or total gastrectomy. The lack of a general desire for food is termed anorexia. This may occur in disease of the stomach or duodenum but it may also be a feature of debilitating disease elsewhere.

Appetite. It is often difficult to distinguish this sensation from that of hunger. It depends to some extent on the smell and memory of food, and appetite is reduced or lost when the sense of smell is destroyed. Loss of appetite may be a feature of gastrointestinal disease and furthermore a revulsion to the smell of food or cooking may be expressed.

Food Habits. These tend to be fixed in an individual and any change may be relevant to the diagnosis. For example, the usual large meal may be avoided because of early repletion. This can be due to disease within the stomach or an anxiety state. Alcohol or fat may be avoided because they cause pain or nausea. Even if these points are not related by the patient, it is necessary to obtain at least a brief dietary history in a patient with a digestive disturbance.

Weight. Weight loss is common in gastrointestinal disease. Usually it is due to a reduced intake of food because of anorexia, nausea or vomiting but it can be due to malabsorption of nutrients or the loss of protein from a diseased bowel as in ulcerative colitis. Occasionally there may be an abnormal gain in weight as in some patients with duodenal ulceration who eat to relieve pain.

Nausea and Vomiting

These are more dramatic symptoms, easy for the patient to describe and of importance in defining the diagnosis. Nausea is an unpleasant sensation, felt in the epigastrium and coming on in waves often associated with salivation, pallor and sweating. It is due to abnormal motility in the upper gastrointestinal tract and particularly to vigorous retroperistalsis in the duodenum. Nausea may proceed to vomiting which is caused by the active contraction of the abdominal wall against a fixed diaphragm with the cardiac sphincter relaxed.

Nausea may be caused by localised disease in the stomach or duodenum and it is often possible to detect a pattern in its occurrence; for example, it may occur first thing in the morning in the alcoholic. Vomiting may result from a variety of stimuli and is not a useful localising symptom. It may occur in diseases of the stomach or small intestine, peritonitis, appendicitis or cholecystitis. Numerous other conditions may be responsible. For example, meningitis, uraemia, migraine and, in the child, infection is a common cause of vomiting. The context of the vomiting is important diagnostically. Sudden vomiting without preceding nausea may be due to direct stimulation of the vomiting centre in the medulla and thus be an indication of intracranial disease. Vomiting in the morning may be due to pregnancy or alcoholic gastritis. The vomiting of large quantities of food and secretions late in the day or at night indicates gastric outlet obstruction. Vomiting which relieves pain is often due to a peptic ulcer. The complaint of persistent vomiting without loss of weight nearly always indicates a psychological disturbance.

Heartburn and Regurgitation

Heartburn is described as a burning retrosternal sensation. Often the patient will indicate that it begins in the epigastrium and radiates up behind the sternum. The sensation must be due to dysmotility or to the oesophagitis which accompanies hiatus hernia. Thus it often accompanies regurgitation of acid gastric contents into the oesophagus but it may occur with slightly acid drinks such as orange juice. Regurgitation is the appearance of previously swallowed food in the mouth without vomiting. The patient complains of an acid or bitter taste because the material usually includes gastric juice. However, in patients with obstruction in the oesophagus, food and saliva may be regurgitated which do not taste bitter. Some patients may describe regurgitation as vomiting but the distinction should be quite clear on taking a careful history. As with heartburn, regurgitation usually signifies that the lower oesophageal sphincter is incompetent as a result of a hiatus hernia.

Waterbrash

Waterbrash is the appearance in the mouth of excessive saliva. It is produced by reflex stimulation of the salivary glands associated with nausea or abdominal discomfort or pain. The mouth fills with saliva either as the direct result of secretion or from regurgitation of saliva from the oesophagus. It is common with the discomfort produced by peptic ulcer. An excessive secretion may also occur in diseases of the mouth and throat and obstruction of the oesophagus.

Dysphagia

This is defined as a difficulty in swallowing. The food is felt to be held up either in the pharynx or at a lower level. Dysphagia is discussed on page 448.

'Wind'

Under normal circumstances a small amount of air is swallowed with food and drink and also when saliva is swallowed. Some of this gas may be expelled up the oesophagus as a belch whilst the remainder passes into the intestines. Some will be absorbed but most, particularly the nitrogen, will be expelled per rectum. It will be seen from the plain X-ray of the abdomen that it is normal for gas to be present in the stomach and colon but very little is present in the small intestine. Some gases, for example carbon dioxide which may be formed in the small intestine, are absorbed but other gases formed in the colon tend to produce an increase in flatus. In the normal individual this may occur with vegetables such as peas or beans.

Patients often complain of 'wind', 'bloating', 'distension', 'belching' and flatus, etc., implying that what they feel to be wrong is an excessive amount of gas in the digestive system. In most cases the patient is misinterpreting the discomfort and excessive gas is not present. The most common cause of excessive gas is swallowing of air (aerophagy) which may be due to anxiety (p. 522), or it may be due to abdominal discomfort caused by an ulcer or other process which induces waterbrash and excessive swallowing of saliva and air. For example the patient may feel full after eating a small amount of food and may assume that this is due to 'wind'. Occasionally, distension of the intestines can be due to fermentation of unabsorbed carbohydrates as in lactose malabsorption.

Constipation and Diarrhoea

These terms have proved difficult to define and again it is important for the physician to be aware of the normal state of affairs. In Britain fewer than 10 per cent of people have less than one bowel motion per day and only 1 per cent have a bowel movement less frequently than three times a week. These latter patients should be regarded as constipated. In addition, if the stool is hard and difficult to pass, the patient should be regarded as constipated whatever the frequency of bowel movement. Similarly, less than 1 per cent of the population have more than three bowel movements per day and this should be regarded as abnormal, particularly if the stool is not formed. When the stool is liquid, or semi-formed it must be regarded as abnormal whatever the frequency of bowel movement. It should be realised that the diet in western countries is low in roughage whereas in countries where a high residue diet is usual, more than three bowel movements per day may be normal.

From this discussion it should be apparent that the physician should ask not only about constipation or diarrhoea but about the number of bowel movements each day, whether defaecation is difficult or painful, the consistency of the stool and most importantly, whether the bowel habit has changed. Even if the patient has diarrhoea, its pattern of occurrence throughout the day is important; for example functional diarrhoea tends to occur on rising in the morning whereas diarrhoea occurring during the night is nearly always indicative of organic disease.

EXAMINATION OF THE ABDOMEN

This must be learned at the bedside. Here the principles of the examination will be summarised.

The mouth and throat are always examined either before or after examination of the abdomen. Particular points to look for are the absence of teeth which may indicate an inadequate diet, infection of the mouth, throat or fauces which can suggest a similar problem in the oesophagus, for example, monilial infection, evidence of vitamin deficiency and tumours of the tongue or lips.

Inspection of the abdomen should be carried out systematically once the patient is comfortably placed in a supine position. The abdomen should move on respiration and be symmetrical. Asymmetry may be due to a mass or enlarged organ. Distension may be due to gas or ascites. Other features to look for are peristalsis and dilated veins.

Palpation. This is commenced away from the area of pain or discomfort. The tone of the muscle is assessed in all four quadrants by gentle palpation. Resistance in one may indicate the site of the problem. Then on deeper palpation, liver, spleen and kidney's are sought and the remaining areas of the abdomen are palpated for masses. No examination is complete without palpation of the hernial orifices.

Percussion of the Abdomen. This is valuable in the distended abdomen in order to decide whether the cause is gas or ascitic fluid.

Auscultation. Auscultation allows an assessment of bowel sounds, an exercise of great value in the acute abdomen (p. 500). In other patients, arterial or venous murmurs or a friction rub from the liver or spleen may be heard.

Rectal Examination. This is an essential part of the examination of the alimentary system.

INVESTIGATION OF THE GASTROINTESTINAL TRACT

Radiology

Radiological techniques form the mainstay of the diagnosis of disease of the alimentary canal and biliary system.

1. **Plain Films.** Plain films of the abdomen are taken prior to other radiological investigations of the alimentary tract and also in patients with acute abdominal pain. Films with the patient erect as well as supine demonstrate any fluid levels within the bowel and air in the peritoneal cavity. On the plain X-ray it is possible to see the normal soft tissue shadows due to the liver, spleen and kidneys and also abnormal shadows. Gas in the intestine acts as a contrast medium so that the distribution of the bowel within the abdomen can be assessed. In obstruction there may be an excessive amount of gas together with fluid levels. Finally, areas of opacification may be due to stones or to calcifica-

tion in the liver, pancreas, cysts or blood vessels and may provide important diagnostic information. A chest X-ray is often helpful in delineating the diaphragmatic areas and in identifying pulmonary lesions from which pain may be referred to the abdomen.

2. **Barium Studies.** In these the gastrointestinal tract is outlined by the use of barium sulphate. This will demonstrate a break in the continuity of the outline of the organ, abnormalities in the appearance of the mucosa and disorders of motility. Preparation of the patient for each examination should always be undertaken so that mucosal detail will not be obscured by contents. For studies of the upper gastrointestinal tract, the patient is fasted and in addition, if pyloric stenosis is suspected, the stomach is washed out to remove food debris. For barium enema studies, the colon should be cleared of faeces by means of laxatives and in some cases by bowel washout just prior to examination.

(*a*) THE BARIUM SWALLOW AND MEAL EXAMINATION. The oesophagus is studied whilst barium is being swallowed. This may demonstrate a disorder of motility, filling defects caused by carcinoma or stricture, or a breakdown in the continuity of the mucosal pattern by varices at the lower end of the oesophagus. Because tumours in the fundus of the stomach may cause obstruction at the lower end of the oesophagus, it is usual to carry out a barium meal at the same examination. Similarly, reflux of gastric contents into the oesophagus may be induced only when the stomach is filled by barium.

The mucosa of the stomach can be examined by using a small amount of barium together with the introduction of air—a double contrast study. More usually, the stomach is filled with a large volume of barium and the contour examined carefully with varying rotation of the patient. The fundus is examined with the patient supine. Ulcers and cancer are seen as an interruption in the barium profile. Various manoeuvres may be necessary to demonstrate a hiatus hernia including the placing of the patient prone over a bolster or supine with the left side raised. Finally, direct observation of the motility of the stomach may indicate an inert area which might be caused by infiltrative disease such as carcinoma. The duodenal cap is also examined by observing the mucosal pattern which may demonstrate folds radiating from an ulcer and by observing the contours of the cap when it is completely filled with barium.

(*b*) THE FOLLOW-THROUGH EXAMINATION. When disease of the small intestine is suspected, barium administered as part of the meal examination is observed during its passage through the small intestine and X-rays are taken at intervals. The outline of the barium may indicate structural abnormalities such as diverticula or strictures. The pattern of the barium is used to judge whether there are abnormalities in the contents of the bowel. For example, when there is malabsorption, the barium may clump and flocculate in the excessive amount of fluid present within the lumen. Sometimes metoclopramide monohydrochloride is given to speed the passage of barium through the small intestine.

(*c*) BARIUM ENEMA. This procedure is uncomfortable and sometimes exhausting for the patient and occasionally patients will suffer from a cardiac arrhythmia when the colon is distended. The elderly and those with established cardiac disease should be admitted to hospital for the procedure. Barium is run into the bowel through a self-retaining catheter inserted into the rectum. X-rays are taken with the whole colon filled with barium in order to see any filling defects or diverticula. In a proportion of patients, barium will reflux into the terminal ileum which can be outlined. Then the patient empties the bowel and further X-rays are taken which show the texture of the mucosa coated by the small amount of remaining barium.

CAUTIONARY NOTE. Exposure to X-rays in the early months of pregnancy may upset normal development of the fetus and be responsible for deformity or still birth. These risks apply not only to radiographic examination of the abdomen such as barium enema but also to procedures such as intravenous pyelograph and X-rays of the lumbar spine and pelvis.

Inadvertent irradiation in the first few weeks of pregnancy can be avoided by restricting radiological examination of the lower abdomen in women of child-bearing age to the 10 days immediately following the onset of the last menstrual period.

3. **Cholecystography.** The gall-bladder is opacified after the ingestion of an iodine containing compound which is excreted in the bile and concentrated in the gall-bladder (p. 569). Since excretion of the compound depends on normal hepatic function, cholecystography will not be successful in the jaundiced patient. After preliminary X-rays of the gall-bladder area, a fatty meal may be given. The X-rays may show a normal gall-bladder or a gall-bladder with stones. The fatty meal releases cholecystokinin which stimulates the gall-bladder to contract and may enable identification of the bile ducts. If the gall-bladder cannot be seen, it is termed ‘non-functioning’. This may be because the contrast medium has not been absorbed from the intestine or excreted by the liver; it may also be due to disease of the gall-bladder which has lost its power of concentration or is obstructed at its neck.

4. **Cholangiography.** An *intravenous cholangiogram* is carried out when oral cholecystography has failed to demonstrate the gall-bladder or when the patient has had cholecystectomy, and to demonstrate the duct system (p. 570). Some patients may have a severe reaction to the iodine and to avoid this, a test dose should be given before the main injection. If the gall-bladder fails to fill with medium, then the cystic duct is blocked. The radiologist assesses the diameter of the common bile duct and will look for filling defects in the duct system which are usually caused by stones.

The *percutaneous transhepatic cholangiogram* (p. 570) is used to outline the duct system when it is suspected that jaundice is caused by extra-hepatic obstruction.

5. **Radiography of the Vascular and Lymphatic Systems.** *Arteriography* is a difficult technique which is utilised occasionally to locate tumours particularly in the liver. In *portal venography* the contrast medium is usually injected directly into the spleen to demonstrate the portal venous system prior to possible surgery for portal hypertension (p. 564). In *lymphangiography* an iodine containing medium is injected into the lymphatics of the foot. This tracks to the

abdominal lymphatics which can be visualised together with their nodes. The technique is used to diagnose intra-abdominal lymphoma.

6. **Radioisotope Studies.** In the pancreatic scan, 75 selenomethionine is used. This aminoacid is taken up by the pancreatic acinar cells and used in the same way as methionine for the synthesis of pancreatic enzymes. Unfortunately selenomethionine is also taken up by the liver and in greater concentration. This makes a pancreatic scan difficult to interpret and a significant proportion of false negative and false positive results occur in the diagnosis of pancreatic tumours and pancreatitis. The procedure is also costly.

Endoscopy

With fibreoptic instruments it is not difficult to examine the whole of the oesophagus, stomach, duodenum and colon. Two bundles of many thousands of fine glass fibres are contained in the instrument's shaft. One bundle carries light to the tip of the instrument in order to illuminate the organ being examined whilst the other has its fibres aligned identically at both ends so that it can transmit an image back to the observer. The fibre bundles are flexible so that the whole shaft can be bent and easily passed into the upper gastrointestinal tract or colon. The shaft of the instrument also carries controls so that the tip of the instrument can be moved, and channels through which air can be passed to insufflate the organ, or forceps to take a biopsy from the mucosa.

Rigid instruments are used to examine the rectum and lower pelvic colon (sigmoidoscope) and occasionally the oesophagus (oesophagoscope).

Examination of the Upper Gastrointestinal Tract. PROCEDURE. A flexible instrument is nearly always used but the rigid hollow oesophagoscope has to be employed to remove a foreign body from the oesophagus or to dilate a stricture by bouginage. It is usual to carry out the procedure with the patient under sedation, often on an out-patient basis. After a 12-hour fast the patient is sedated and the pharynx is anaesthetised with a xylocaine spray or lozenge. The instrument is passed with the assistance of the patient in swallowing and the procedure, whilst uncomfortable, should be no more so than any other intubation. Possible complications are perforation of the oesophagus whilst passing the instrument or during biopsy, and the inhalation of secretions. Fortunately these are rare.

OESOPHAGOSCOPY. This is always carried out when there is dysphagia or when the barium swallow suggests that a tumour or a stricture is present. Relative indications include suspected oesophagitis, varices or the presence of a motility disorder since this might be associated with a tumour.

GASTROSCOPY. This is indicated when a gastric ulcer has been demonstrated on barium studies so that a biopsy can be taken in case the ulcer is malignant. Healing of the ulcer should be assessed by further gastroscopy. Other suspicious areas on the barium study can be seen and biopsies taken. Gastroscopy is nearly always necessary in the assessment of patients with symptoms after gastric surgery because the appearances are difficult to assess radiologically.

DUODENOSCOPY. This is indicated when there are unexplained abnormalities on the barium study. It is sometimes possible to cannulate the ampulla and inject dye into the pancreatic duct system but this is a difficult procedure.

PANENDOSCOPY. At most examinations it is usual to examine the oesophagus, stomach and duodenal cap with the same instrument. This is because the presence of one lesion does not exclude another and double lesions are common, e.g. hiatus hernia and duodenal ulcer. Panendoscopy is also carried out as an emergency procedure on patients with haematemesis and melaena, once the stomach has been cleared of blood and clot by gastric lavage. It is also invaluable in patients with radiologically negative dyspepsia since an abnormality is often found which could not have been identified otherwise.

Examination of the Lower Gastrointestinal Tract. PROCTOSCOPY AND SIGMOIDOSCOPY. These are simple procedures which should always be carried out in patients with bowel disturbance or other symptoms referable to the lower bowel or anus. Both terms are inaccurate since proctoscopy visualises the anal canal and only 2-3 cm of the rectum, and sigmoidoscopy examines the rectum and the lower few centimetres of the pelvic colon. It is usual to carry out the procedure without preparation but if the rectum contains faeces, then the examination is repeated at a later date after the bowel has been emptied. The examination is carried out with the patient in the knee-elbow position, or on the left side with the knees drawn up. The anus is always dilated by the finger and the instrument should be warmed and well lubricated. Proctoscopy is used for the demonstration and injection of haemorrhoids. Sigmoidoscopy is necessary for the diagnosis of polyps, cancer of the rectum, ulcerative proctitis and Crohn's disease of the large bowel. Sigmoidoscopy must be carried out under anaesthesia when there is a painful condition of the anus such as a fissure; it should be avoided in fulminating ulcerative colitis because of the danger of perforation.

COLONOSCOPY. The flexible colonoscope allows examination of the whole colon but the procedure is time-consuming and occasionally difficult. The bowel must be carefully prepared over several days, first with laxatives and then by lavage so that no faecal material remains. The procedure is the only alternative to laparotomy in patients who on barium enema examination, show changes which could be due to carcinoma.

Biopsy and Cytology

Biopsy of lesions is an essential part of each endoscopic procedure and biopsy of an apparently normal mucosa can also provide important diagnostic information. Apart from rectal biopsies the only problem with biopsies taken at endoscopy is their small size which makes interpretation by the pathologist difficult.

Biopsy of the Small Intestine. This is carried out by means of the Crosby capsule. After an overnight fast the capsule is passed into the jejunum attached to a stiff radio-opaque catheter and the biopsy is taken just distal to the duodenojejunal flexure. Suction via the catheter draws mucosa into a small port on the side of the instrument. The negative pressure which develops within the capsule also fires the knife which severs the mucosa. The intubation and biopsy are completed in about one hour. Complications are rare. Bleeding occurs occasionally and for this reason biopsies should not be carried out unless the platelet count and prothrombin time are normal. Another complication is perforation of the intestine.

The biopsy specimens are inspected under the dissecting microscope immediately after they are recovered from the capsule. Intestinal biopsy is indicated whenever malabsorption is suspected.

Cytological Studies. These are not widely used in gastroenterology because the cytological appearances are difficult to interpret and require the services of an expert cytologist. However, gastric cytology can be an accurate method for the diagnosis of gastric cancer. The patient is fasted for 12 hours and a nasogastric tube is passed into the stomach and a vigorous lavage with saline is carried out. The fluid is aspirated, centrifuged and the sediment is spread on to slides for examination by the pathologist.

Secretory Studies

Intubation of the upper gastrointestinal tract may be carried out for gastric or pancreatic function tests and to aspirate secretions for bacteriological studies.

Gastric Function Tests. 1. THE PENTAGASTRIN TEST. The acid output is measured in response to a gastric stimulant, pentagastrin, a synthetic pentapeptide which exerts the biological effects of gastrin. Preparation consists of an overnight fast. A barium meal examination should not be performed on the day before the test because some barium might remain in the stomach. Anticholinergic drugs must be stopped for at least 48 hours since they will suppress acid secretion. A soft, radio-opaque tube is passed through the nose or mouth and its tip is positioned by fluoroscopy at the middle of the greater curvature of the stomach. The patient is placed supine and tilted slightly to the left. The fasting contents are aspirated and their volume measured and then the secretions are collected continuously for one hour. This is termed the 'basal acid output'. Then pentagastrin is given subcutaneously in a dose of 6 μg/kg body weight and the secretions are collected for a further hour. The acid output in this hour is termed the 'maximum acid output'. Acid outputs are calculated from the volume of secretion and the concentration of acid as assessed by titration to pH 7.

The pentagastrin test is important because:

(*a*) The presence of achlorhydria can be demonstrated. Achlorhydria means absence of hydrochloric acid in the gastric juice; it is said to occur when the pH of the gastric juice does not fall below 6 after stimulation with pentagastrin. The demonstration of achlorhydria is important in the diagnosis of pernicious anaemia.

(*b*) An increased volume of fasting juice is often an indication of pyloric stenosis.

(*c*) A very high basal acid output may indicate that the patient has the Zollinger-Ellison syndrome (p. 470).

(*d*) In patients with peptic ulcer, the level of the acid output may influence the choice of operation.

2. THE INSULIN TEST. This test is used after gastric surgery to indicate the completeness of vagotomy. The preparation and procedure are similar to those described above but the gastric stimulant is soluble insulin which is given intravenously. The resulting hypoglycaemia stimulates the vagal centres and gastric acid is secreted if the vagal innervation of the stomach has not been completely divided.

Pancreatic Function Tests. Pancreatic function is tested by passing tubes into the stomach and duodenum under radiological control. The gastric juice is aspirated throughout the test so that it does not mix with the pancreatic secretions. Secretin and pancreozymin are given by intravenous injection and the pancreatic secretions are collected for one hour. Measurements are made of the volume of secretion, the bicarbonate concentration and the concentration of amylase or trypsin.

The test is used to demonstrate pancreatic insufficiency, when there is a low volume of secretion and a reduction in the concentration and output of bicarbonate and enzymes. It is sometimes possible to distinguish chronic pancreatitis from carcinoma and the test is also of use in excluding pancreatic disease as a cause of malabsorption. However, its value is limited because of the technical difficulties involved and because early disease of the pancreas may not be detected.

Bacteriological Studies

The malabsorption syndrome may be due occasionally to the overgrowth of bacteria (p. 491). When this is suspected, secretion can be obtained for bacteriological studies by passing a fine sterile tube into the upper small intestine. A mercury bag attached to the tip of the tube ensures that the tube moves rapidly to the correct site. The patient should not be receiving antibiotics.

Motility Studies

The barium meal gives a rough idea of the motility of the oesophagus, stomach and small intestine. On occasion cineradiology may be used and this is particularly helpful in the analysis of dysphagia.

Motility can be studied more accurately by measuring the pressure changes in the lumen of the organ but only in the case of the oesophagus is this of diagnostic value. Fine open ended tubes are passed into the stomach and pressures are transmitted to transducers and measured at intervals whilst the tube is gradually withdrawn with the patient swallowing. The procedure may be of value in establishing the relationship between chest pain and abnormal oesophageal contractions, for the diagnosis of motility disorders of the oesophagus, in determining the position of the oesophageal sphincter when there is a hiatus hernia and in studying disorders of the large bowel, e.g. diverticular disease.

Examination of the Stool

Visual Examination. In malabsorption the stool may be pale and frothy, in the irritable bowel syndrome it may be like pellets or ribbon and with or without mucus. In mild ulcerative disease of the colon there may be flecks of blood in the mucus. Inspection of the stool is sufficient to diagnose fresh bleeding from the lower alimentary tract while the loss of over 60 ml of blood from a site proximal to the ascending colon will produce a black tarry stool.

Occult Blood Tests. In order to detect small amounts of blood it is necessary to use a chemical test which depends on the presence of haematin. Stools should be collected on several successive days for occult blood testing. Specimens obtained on the finger-stall at rectal examination can readily be examined.

Microscopic Examination. This is of value particularly in distinguishing amoebic dysentery and other parasitic diseases and in pancreatic insufficiency in children (p. 481).

DISEASES OF THE MOUTH

The mouth acts as a receptacle in which food can be broken down into small particles during mastication. Into the mouth flows the saliva which is secreted in response to the sight, taste and smell of food, and also to the act of chewing. Saliva has several functions. It facilitates speech, moistens the food and lubricates the process of swallowing. By its solvent action on the foodstuffs, it enables tasting to take place. It also contains an enzyme ptyalin which is concerned in the digestion of polysaccharides to disaccharides.

The Teeth

The reduction of food to a soft pulp by efficient mastication is an important prerequisite to good digestion. It is essential therefore to determine whether the patient has an adequate number of teeth, and whether those that are present are directly in apposition in the lower and upper jaw. If dentures are used, they must be comfortable, otherwise they may be worn only for the sake of appearances, and removed at mealtimes. Oral sepsis is not only an unpleasant social condition, but it may also predispose to disease. Respiratory infection may result from the inhalation of septic material or micro-organisms from the mouth, and bacteraemia may have its source in dental disease such as ulcerative stomatitis or a periapical abscess. Bacteraemia from these sources is particularly liable to occur after dental manipulation and may cause bacterial endocarditis in patients with valvular disease of the heart; for this reason such patients should always be given prophylactic injections of penicillin both before and after dental extraction (p. 96). All patients should be advised to consult a dentist regularly in order to conserve the teeth and to prevent or treat foci of infection in the mouth.

Stomatitis

Stomatitis, or inflammation of the mouth, is of several varieties; it may involve the gums (gingivitis), the lips (cheilosis), or the angles of the mouth (angular stomatitis).

Non-specific gingivitis and stomatitis. The mouth harbours a dense population of commensal micro-organisms. Normally, this microbial population is controlled by a reasonable standard of oral hygiene; if this is neglected the bacterial population may proliferate on the cervical margins of the teeth and cause gingivitis or a more generalised stomatitis. Non-specific gingivitis and stomatitis may also occur when resistance to the commensal population is altered by febrile illness, wasting diseases, or by blood dyscrasias. It occurs particularly when the mouth is not cleaned regularly. The gums are swollen and painful and the mucous membrane is reddened. In those patients with severe illness, the mouth should be washed repeatedly (p. 56). In otherwise healthy people, non-specific gingivitis may be treated and controlled by proper oral hygiene and if necessary by dental procedures such as scaling and polishing. The anticonvulsant drug phenytoin (p. 444) may cause hypertrophic gingivitis, in which the gums become hypertrophied and encroach on the teeth.

Stomatitis due to Deficiency of Nutritional Factors. This may arise directly from an insufficient intake of essential food factors (pp. 160 and 170) or indirectly as a result of impaired absorption (pp. 489 and 490). This form of stomatitis may be caused by deficiency of the B group of vitamins, especially niacin, riboflavin, folic acid, and cyanocobalamin, and it may also be caused by long-standing iron deficiency. Thus, stomatitis is a characteristic feature of such deficiency diseases as pellagra, pernicious anaemia, and severe chronic iron deficiency anaemia. When the deficiency is acute and severe, the tongue is red, raw and painful. When the deficiency is chronic and less severe the tongue appears moist and unduly clean because of atrophy of the papilla. Angular stomatitis often accompanies glossitis, especially in the case of severe iron deficiency. Severe vitamin C deficiency is characterised by gingivitis so that the gums become swollen and spongy and bleed readily.

Ulcerative Stomatitis (Vincent's angina). This occurs mainly in adults in conditions associated with malnutrition and poor dental hygiene; it is not commonly seen nowadays in Britain. Ulcers with ragged necrotic margins occur especially on the gums, but may involve the palate, the lips, or the inner aspects of the cheeks; the ulcers are covered by a grey slough surrounded by an erythematous margin. A direct smear of these ulcers reveals numerous fusiform spirochaetes (Vincent's organisms); these organisms are present in small numbers in the normal commensal population of the mouth and the condition may be regarded as an endogenous infection due to proliferation of the spirochaetes because of some alteration in host resistance. The condition is infectious, so that the patient's food vessels and cutlery should be sterilised. The acute phase responds to local treatment with metronidazole (Flagyl) in a dose of

200 mg three times per day for three days, or to penicillin. Necrosis of the gums may occur, so that when the acute phase has been controlled it is most important that proper dental treatment is undertaken; surgical correction of the deformities resulting from tissue necrosis may be necessary.

Oral Candidiasis. The fungus *candida albicans* is a normal commensal in the mouth but it may proliferate to cause frank infection as a result of the prolonged use of antimicrobial agents, during treatment with corticosteroids, or in patients with severe debilitating illness; it may occur in infants if the feeding bottles are not sterilised properly. White sloughs covering areas of superficial ulceration appear on the gums, palate and cheeks, and they enlarge and coalesce to form an easily detached membrane. In severe infection, the lower pharynx and oesophagus may be affected, causing dysphagia. The condition may be treated by painting the oral cavity with 1 per cent aqueous solution of gentian violet, three times a day for four days. If the condition is at all severe, tablets containing 500,000 units of nystatin should be sucked and retained in the mouth for as long as possible, and should be given four times daily for seven days. Every attempt must be made to improve the nutrition of the patient.

Aphthous Stomatitis. This is a common condition which is characterised by the development of one or more ulcers in the mouth; the lesion begins as a small vesicle which then develops into a shallow or occasionally a deep ulcer. The ulcers are often multiple, and may occur in crops. Apart from the fact that the condition may follow periods of emotional stress, the aetiology is unknown. Aphthous stomatitis may occur in association with various gastro-intestinal disorders such as ulcerative colitis, but more commonly there is no obvious physical disease. The condition is extremely painful and does not readily respond to therapy. In general, treatment should be limited to the local application of balsamic resins such as a tincture of benzoin paint to relieve pain. Secondary infection may be controlled by the use of a 2 per cent chlortetracycline mouthwash for not more than seven days. Some patients may gain relief by sucking pellets of 2·5 mg hydrocortisone or local anaesthetic.

Allergic Stomatitis. Stomatitis can also result from an allergic reaction to certain chemicals as in toothpaste, dentures or mint sweets, or to antibiotics especially if they have been used locally. It may also occur in angioneurotic oedema.

Metals such as bismuth, mercury, gold or arsenic may rarely cause stomatitis. A characteristic blue-black line may be seen where the gum margins adjoin the teeth in lead poisoning. Treatment of the stomatitis consists of removing the patient from exposure to the metallic poisons, or stopping their administration. In severe cases dimercaprol (p. 776) should be given.

Skin diseases such as lichen planus, pemphigus, and erythema multiforme commonly involve the mouth and sometimes the oral manifestations may precede the general development of these conditions.

The Tongue

In health the tongue is moist with only a slight white fur on the dorsum. The papillae are readily seen. Mouth breathing causes a dry tongue, but otherwise dryness of the tongue is an indication of dehydration.

The tongue may be coated with a whitish-yellow fur in persons who smoke excessively. The tongue is dry and covered with a dirty brownish fur in febrile diseases. In general, the presence of fur on the tongue has little clinical significance.

Glossitis. Acute or more usually chronic glossitis, may be a prominent feature of stomatitis resulting from nutritional deficiency (p. 444).

Simple Ulceration of the Tongue. This may occur in association with various forms of stomatitis, or as a result of trauma from the sharp edges of damaged teeth, badly fitting dentures or biting during epileptic fits.

Chronic Ulceration of the Tongue. In all cases of chronic ulceration of the tongue it is essential to exclude a carcinoma and if any doubt exists biopsy should be carried out.

Syphilis of the Tongue. This may occur as a primary chancre, in the secondary stage as 'mucous patches', or in the tertiary stage as painless gummatous ulcers. All of these manifestations are now rare in Britain.

Leukoplakia of the Tongue is a chronic affection characterised by the presence of white, firm, smooth patches beginning at the side of the tongue and later spreading over the dorsum. In the early stages the tongue is not painful but later the patches are split by fissures with resultant pain and tenderness. The importance of leukoplakia is that it may precede the development of carcinoma, and a biopsy of such lesions should always be undertaken.

Psychogenic Pain. The patient complains of a persistently painful tongue but the tongue is normal on inspection and the pain has no relation to substances such as vinegar or hot liquids as occurs with a true glossitis. The psychological origin of these symptoms is usually obscure and the complaint amounts virtually to a delusion. The symptom is often intractable.

The Salivary Glands

Excessive salivary secretion may be a response to irritation or inflammation in the mouth, e.g. oral sepsis, or it may develop reflexly as in trigeminal neuralgia; it is an important symptom in oesophageal obstruction. An increased amount of saliva may be secreted in post-encephalitic Parkinsonism (p. 873). Certain drugs such as potassium iodide and the heavy metals, are excreted in the saliva and this may cause an increased secretion.

Treatment depends on removal of the underlying cause. Symptomatic treatment consists of the administration of drugs such as atropine which inhibit parasympathetic action.

Xerostomia

Xerostomia is usually defined as a deficient secretion of saliva though a dry mouth may be seen in mouth breathers and in persons who sleep with the mouth open. The condition is most commonly found to be associated with acute febrile conditions, and in states of marked dehydration, such as diabetes mellitus, or when severe diarrhoea is present. Xerostomia, due to disease of the parotid gland and associated with defective lachrymation, is one of the features of Sjögren's syndrome (p. 778). As already noted, anticholinergic drugs will depress salivary secretion.

Treatment consists of measures to treat the fever and cure the dehydration. Symptomatic treatment consists of the use of acidulated sweets, chewing gum, bitter tonics before meals, and very exceptionally the use of cholinergic drugs such as pilocarpine which may be required to stimulate salivary secretion when all other methods have failed. In the treatment of patients with early Sjögren's syndrome corticosteroids have been shown to cause the return of normal salivary secretion.

Parotitis

Inflammation of the parotid glands may be due to the virus of mumps (p. 87) or to bacterial infection of the glands. The latter tends to develop during severe febrile illnesses and after major surgical operations if adequate attention is not given to careful oral hygiene and to the prevention of dehydration and toxaemia. Septic parotitis is much more rarely encountered today than formerly. Its treatment consists of the parenteral administration of penicillin and surgical drainage if abscess formation has occurred. Enlargement of the parotid glands may be noted in patients with sarcoidosis.

Salivary Calculi

Calculi occur occasionally in the submandibular gland or its duct. They cause pain and swelling brought on by eating. Infection of the gland is a complication. Stones in the duct can be felt in the floor of the mouth and can be removed by incision over the duct. Stones in the body of the gland may require excision of the gland.

Tumours

The only common tumour is the mixed salivary tumour which presents as a slow, painless enlargement of one parotid gland. The tumour shows a variable degree of malignancy and is treated by excision.

DISEASES OF THE OESOPHAGUS

The oesophagus is a muscular tube extending from the pharynx to the cardia. It has two functional sphincters, one at the junction with the pharynx, the other at the junction with the stomach. It is closely related in the chest to the aorta, the left main bronchus and the left atrium. The musculature of the upper oesophagus is striated, but lower down the muscle is smooth. The oesophagus is lined with squamous epithelium although glandular elements may be found towards the lower end or may occur as islets at irregular points along its length.

Dysphagia

Dysphagia is defined as difficulty in swallowing. Since the only function of the oesophagus is the transmission of food from mouth to stomach, most diseases of the oesophagus and its adjacent structures produce dysphagia.

Causes of Dysphagia

1. PAINFUL DISEASES of the mouth and pharynx, e.g. stomatitis, tonsillitis, quinsy, tuberculous laryngitis, retro-pharyngeal abscess, produce dysphagia, the cause of which is readily apparent.

2. NEUROLOGICAL DISTURBANCES of deglutition, e.g. as a result of bulbar and pseudo-bulbar paralysis, diphtheric neuritis or myasthenia gravis, or disorders of oesophageal motility, as in achalasia and oesophageal spasm, are not uncommon.

3. EXTRINSIC COMPRESSION of the oesophagus, as from a goitre, aortic aneurysm, cardiac enlargement or pericardial effusion; or from enlarged mediastinal lymph nodes, secondary to a lymphoma or carcinoma of the breast or bronchus. Dysphagia from such causes is rarely a presenting symptom and the underlying cause is usually apparent.

4. INTRINSIC DISEASE OF THE OESOPHAGUS:

(a) *Congenital Abnormalities.* Atresia, the upper oesophagus ending blindly at about the level of the tracheal bifurcation, occurs occasionally requiring urgent surgery in the newborn. A short oesophagus with hernia and stricture can occur as congenital abnormalities, though most examples are probably due to acquired disease.

(b) *Ulceration.* Oesophagitis is most commonly due to reflux of gastric contents through a sphincter made incompetent by a hiatus hernia. There is acid-pepsin digestion of the oesophageal mucosa immediately above the hernia, with ulceration, spasm and eventual stricture formation.

Oesophagitis and stricture are occasionally caused by the ingestion, accidental or otherwise, of corrosives such as bleach or caustic soda.

(c) *Tumour.* Carcinoma of the oesophagus or of the cardia of the stomach is the usual cause of dysphagia in elderly patients with no preceding history of indigestion or heartburn.

5. OTHER CAUSES OF DYSPHAGIA. These include sideropenic dysphagia (p. 722) and scleroderma (p. 782). 'Dysphagia' also occurs in association with psychological stress, e.g. globus hystericus (p. 523).

Methods of Examination

The exclusion of malignant disease is essential in the investigation of any patient who complains of dysphagia. Barium swallow and oesophagoscopy are required (p. 439). Where the disorder appears to be one of function rather than structure, as for example an upset of the oesophageal sphincter mechanisms, then both manometry and cineradiography can give valuable additional information.

The demonstration of disordered oesophageal motility by manometry is of diagnostic significance in such conditions as achalasia and scleroderma.

Sideropenic Dysphagia

(PLUMMER-VINSON SYNDROME)

This form of dysphagia is mostly seen in middle-aged or elderly women and is associated with iron deficiency anaemia, glossitis, diminished gastric secretion, and perhaps koilonychia and splenic enlargement.

There is degeneration and atrophy of the epithelium of tongue, pharynx, oesophagus and stomach. The actual cause of the dysphagia is believed to be spasm at the entrance to the oesophagus. Here, too, a film or fold of degenerating epithelial cells—the 'post-cricoid web'—may be demonstrable radiographically or endoscopically. The dysphagia is to solids rather than liquids, is intermittent, and may therefore mistakenly be thought to be hysterical.

Treatment. The dilatation associated with the diagnostic endoscopy is often sufficient to relieve symptoms. Iron therapy is given. Such patients should remain under periodic review, because the anaemia may recur and the mucosal degeneration may predispose in later years to the development of post-cricoid carcinoma.

Oesophageal Hiatus Hernia and Reflux Oesophagitis

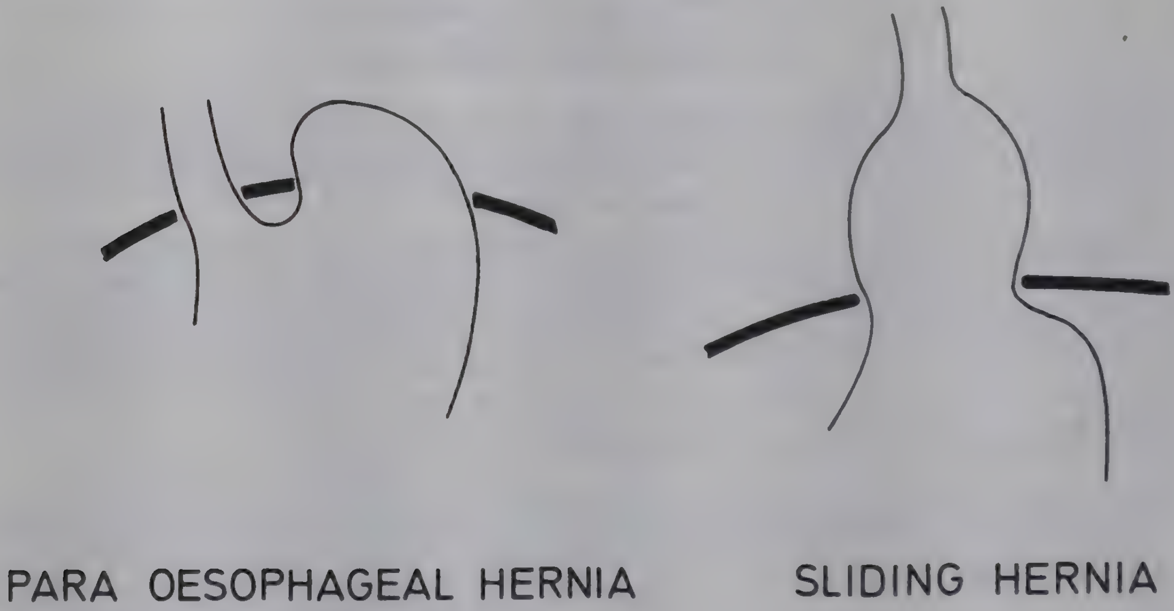
The oesophageal hiatus is the most important of the openings in the diaphragm through which herniation of abdominal viscera into the thorax can occur. Normally once a bolus has been propelled into the stomach it does not reflux into the oesophagus. The mechanism of the valvular junction between oesophagus and stomach is not clearly understood. In part it may depend on the presence of a physiological sphincter in the lower oesophagus and in part also on the angle of entry of the oesophagus into the stomach. When this is altered, as in herniation of the oesophago-gastric junction through the oesophageal hiatus in the diaphragm, there may be reflux of gastric content into the oesophagus despite the physiological sphincter.

If reflux continues over any lengthy period, the exposure of the lower oesophageal mucosa to the irritant effects of gastric juice results in oesophagitis. Occasionally such reflux takes place in the absence of a demonstrable hiatus hernia.

Herniation of the intra-abdominal oesophagus and adjacent stomach may be found at any age, but it is most frequent in middle-aged and elderly patients.

The two important types of hiatus hernia are:

1. PARA-OESOPHAGEAL OR 'ROLLING' HIATUS HERNIA. Here a knuckle of stomach herniates alongside the oesophagus through the hiatus (Fig. 62). The lower oesophageal sphincter remains competent and below the diaphragm even in extreme cases when most of the stomach rotates to follow the herniated knuckle into the chest. A large hernia in the posterior mediastinum will lead to cardiac arrhythmias and breathlessness. Occasionally symptoms become acute because of obstruction, distension and even gangrene of the herniated portion of stomach and then surgery may be required urgently. Otherwise, and as a planned procedure, surgical repair of the hernia may be required.



PARA OESOPHAGEAL HERNIA

SLIDING HERNIA

FIG. 62

Hiatus hernia.

2. OESOPHAGO-GASTRIC OR 'SLIDING' HERNIA. In this variety, the oesophago-gastric junction herniates into the thorax and there is free gastric reflux. This is the most common form of hiatus hernia (Fig. 62).

Aetiology. Both types of hernia are more common in women than men. The incidence of hernia tends to increase with age probably because of weakening of the diaphragmatic muscle. An increase in intra-abdominal pressure, as occurs in pregnancy, obesity or ascites will predispose to its development.

Clinical Features. Heartburn is the characteristic symptom of reflux oesophagitis. It is a deeply placed 'burning' pain, felt retro-sternally and brought on by bending, stooping or by the exertion of lifting or straining with consequent increase in intra-abdominal pressure. It may also occur on lying down at night. It wakens the patient who finds that he can gain relief by sitting up, or by taking food or alkali. When severe, some patients find it more comfortable to spend the night in an easy chair. No other pain produced in the alimentary tract is so closely linked to change of posture as that of reflux oesophagitis.

Nevertheless, because of its relation to exercise, it may be confused with angina pectoris, because the substernal pain of reflux oesophagitis may radiate upwards and to the left arm in the same way as pain of cardiac origin. In these patients, an exercise ECG and an attempt to reproduce the symptoms by perfusing acid into the oesophagus may be needed to establish the diagnosis.

The nocturnal pain of reflux oesophagitis, awakening the patient from sleep, can be confused with the hunger pain of duodenal ulcer. Posture has no effect on the latter, which comes on later in the night, but some patients suffer both types of pain because duodenal ulcer and hiatus hernia may co-exist. Confusion here is of less import than in the case of coronary artery disease. The management and particularly the prognosis of duodenal ulcer and hiatus hernia are similar, whereas a patient mistakenly thought to have heart disease may suffer needless restrictions.

Once a stricture has developed, the oesophagitis becomes less acute and the pain diminishes or disappears, because the narrowing tends to protect the oesophagus from reflux. For a time the patient believes cure to be imminent, but he is disillusioned when he discovers that swallowing becomes increasingly difficult.

Unless they give rise to significant reflux, to oesophagitis or to dysphagia, many hiatus hernias remain symptomless. Some patients may present with severe anaemia due to blood loss from the inflamed oesophagus and of those who do, about one-third have no other symptom. Oesophagitis should therefore be sought in persistent and unexplained iron deficient anaemia.

Occasionally there is frank bleeding due to the development of an ulcer in the herniated portion of stomach and this may at times require emergency treatment.

Diagnosis. Careful analysis of the patient's pain to elicit its relation to posture and stooping, its response to the measures outlined above with perhaps the later onset of dysphagia is sufficient to allow a clinical diagnosis to be made. Physical examination is unrewarding except to indicate obesity, but not all sufferers are fat. Confirmation of the diagnosis depends on radiological examination with barium (p. 437) and oesophagoscopy is necessary to diagnose the presence of oesophagitis; oesophagoscopy will also exclude the presence of other lesions in the vicinity of the hernia, such as a small gastric carcinoma or an ulcer.

Treatment. The majority of patients with reflux oesophagitis have relatively mild symptoms which can be controlled by medical treatment. The most important single measure is reduction of weight in patients with obesity (p. 177). Meals should be small and well masticated. Women should avoid wearing corsets and tight garments. The head of the bed should be elevated on blocks and the patient should be taught to sleep in a semi-upright position. In the acute stage, an ulcer regime with bland diet and antacids particularly last thing at night should be recommended. During the day, stooping and bending from the waist is to be avoided. Anaemia will usually respond to oral iron, although where there is obvious blood loss, blood transfusion may be indicated.

Failure to respond to these measures is more likely in thin subjects, while the restrictions imposed on activity and the enjoyment of life by the continued adherence to a strict medical regime prove unacceptable to some.

Persistent oesophagitis and stricture formation are indications for surgery. This includes repair of the hernia, reconstitution of the valve mechanism, an acid reducing procedure (p. 464) and the treatment of concomitant duodenal ulcer where indicated. Stricture will usually respond to these measures, supplemented by bouginage in the post-operative period; if it does not, resection is occasionally required.

Traction Diverticulum

The most common site for a traction diverticulum is in the anterior wall of the oesophagus just below the level of the tracheal bifurcation. It is due to chronic inflammation, usually tuberculous in related lymph nodes. By the time the diverticulum is discovered, often accidentally during barium swallow, the disease in the lymph nodes has healed. It is seldom that the diverticulum itself causes symptoms and surgical treatment is rarely necessary.

Pharyngeal Pouch

This diverticulum develops at the site of the inferior constrictor of the pharynx. It begins as a posterior bulge of mucosa which enlarges to form a sac that extends downwards and to the left between oesophagus and cervical spine.

The fully-formed sac causes dysphagia due to displacement forwards of the cervical oesophagus and its ostium. There is swelling and gurgling in the neck on swallowing. The patient may present with recurrent attacks of stridor or inhalation of contents of the sac may lead to pneumonia.

The condition is seen almost exclusively in middle-aged subjects. For long it was thought to be due to a congenital weakness between the two components of the inferior pharyngeal constrictor, but its late onset and the fact that dysphagia *precedes* the formation of the pouch indicate that the condition is the result of muscle incoordination.

Treatment is surgical, a one-stage resection of the pouch with careful suture of its neck being carried out after preliminary cleansing and under antibiotic cover. The danger is leakage or contamination with consequent mediastinitis.

In Edinburgh, pharyngeal pouch is remembered as the affliction of Lord Jeffrey (1773–1850), a Scottish judge and wit, who, in these days before operation, emptied his pouch with a specially designed silver spoon.

Achalasia of the Cardia

(CARDIOSPASM)

Although apparently confined to the lower end where there is failure of the sphincter to relax, this is in fact a motility disorder of the whole oesophagus which shows progressive atony and dilatation. The cause is probably a failure of nerve conduction due to diminution in the number of ganglion cells. In South America, Chagas' disease—an infection with a trypanosome—produces similar changes (p. 974).

Clinical Features. The dysphagia of achalasia is insidious and at first amounts to little more than a slowness in swallowing which the patient may accept as normal and not seek medical advice. With increasing dysphagia, the site of obstruction is felt to be behind the lower end of the sternum. Until a late stage the patient continues to eat food of reasonable variety and amount, the excess accumulating in the capacious non-contractile oesophagus. Putrefaction of the retained residue leads to an offensive smell in the breath, while inhalation may occur silently at night to cause recurrent pulmonary infection.

Radiology. A chest X-ray may be sufficient to show an enlarged oesophageal outline, perhaps with a fluid level behind the heart shadow.

A barium swallow shows the dilated atonic oesophagus coming to a smooth pointed termination. There is absence of the usual gas shadow in the fundus of the stomach.

While the appearances are typical, they are not diagnostic because they can be mimicked by a carcinoma at the lower end of the oesophagus or in the cardiac portion of the stomach. Treated or untreated, patients with achalasia have an increased liability to carcinoma of the oesophagus which makes initial endoscopy essential and periodic review after treatment desirable.

Manometry. This may be of value in defining the diagnosis since some other conditions may have a similar radiological picture.

Oesophagoscopy. Oesophagoscopy should always be carried out. Usually cleansing of the oesophagus with mechanical removal of the larger retained food fragments is required and this may involve repeated lavage, aspiration and oesophagoscopy. Once the oesophagus is clean, its wall can be inspected, its termination studied, bougies passed and biopsies taken.

Treatment. Treatment may be by dilatation or cardiomyotomy. When the choice is dilatation, a bougie is passed through the lower end of the oesophagus and a distensible bag guided through the narrowed segment. Using water pressure, the bag is forcibly distended in order to split the circular muscle fibres of the oesophagus. A single dilatation may cure the patient. If not, it can reasonably be repeated.

Failure of hydrostatic dilatation or inability to introduce the bougie or dilator are indications for operation, which takes the form of cardiomyotomy (Heller's operation). Here the muscle at the lower end of the oesophagus and for some distance above and below is slit to expose but not to penetrate the mucosa. The operation can be performed through the chest or the abdomen and is relatively effective and safe, even in the elderly. Both procedures may be followed immediately by reflux oesophagitis or oesophageal perforation.

Diffuse Spasm of the Oesophagus

Like achalasia, diffuse spasm is probably caused by a disorder in Auerbach's plexus. Often there is hypertrophy of the muscle wall of the oesophagus.

The main symptom is pain precipitated by eating or by emotional stress. The pain is retrosternal and there may be radiation to the back, neck or arms, thus making the differential diagnosis from coronary artery disease difficult. The pain may or may not be accompanied by dysphagia. The diagnosis is established by barium swallow which shows a hold-up of barium in the oesophagus due to multiple uncoordinated contractions. The appearance resembles a 'corkscrew'. Manometry confirms the lack of a coordinated peristaltic wave.

Treatment involves education in eating in a relaxed atmosphere with adequate mastication. Nitroglycerine may relieve pain. Since most patients are over the age of 60, the physician has to persist with medical management but in the occasional younger patient, an extended cardiomyotomy may be required.

Carcinoma of the Oesophagus

Carcinoma of the oesophagus occurs mainly in men and at a later age than other cancers. It has some association with smoking, the consumption of spices and spirits, with achalasia, and more especially with race.

In the western hemisphere, the most frequent site of carcinoma is the lower third of the oesophagus; it is less common in the middle third and least common in the upper third. The lesion is usually ulcerative in form, and it extends circumferentially and longitudinally in the wall of the oesophagus. Direct invasion of surrounding structures and involvement of related lymph nodes is common by the time of diagnosis. Histologically the growth is squamous celled. Where an adenocarcinoma is found, it has probably spread from the stomach to invade the lower oesophagus. Rarely primary adenocarcinoma of the oesophagus occurs which is presumed to originate in submucosal glandular elements.

Clinical Features. Progressive dysphagia is typical. It starts with the 'sticking' of solid food, at first intermittently and then regularly and proceeds to difficulty with semi-solids and eventually with liquids. There is discomfort, not amounting to pain at the site of the obstruction which is usually well localised by the patient. The development of symptoms occupies some months so that by the time the patient first attends, weight loss is already a feature.

Diagnostic physical signs are those of metastases to lymph nodes, liver and related structures in the mediastinum.

Radiology. Obstruction and an irregular narrowing of the oesophagus are highly suggestive of the diagnosis (Fig. 63). At the lower end it may not be possible to distinguish between carcinoma of the oesophagus and carcinoma of the cardia. Oesophagitis and a benign stricture may simulate carcinoma and the differentiation is rendered more difficult when a hiatus hernia is present.

Oesophagoscopy. Endoscopy should always be carried out and it provides an opportunity of removing tissue for histological examination. Repeated biopsy may be required to obtain positive confirmation of the diagnosis, and this is particularly so when stricture formation prevents further passage of the oesophagoscope or the biopsy forceps. In these circumstances, the passage of a brush through the narrowed area and examination of dislodged cells is of value.

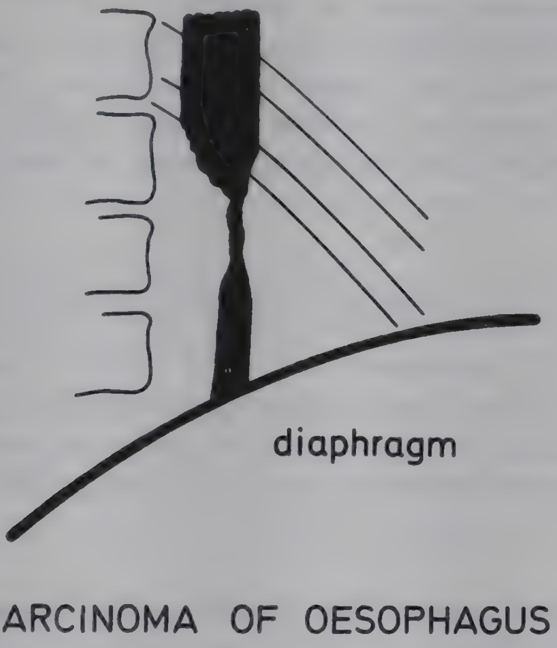


Fig. 63
X-ray of carcinoma of oesophagus.

Treatment. The choice lies between palliation and radical treatment. The chances of cure seldom exceed 10 per cent. In squamous carcinoma, particularly of the upper and middle thirds, high voltage radiotherapy is the treatment of choice in those centres possessing the necessary facilities.

Otherwise, and with tumours of the lower third, oesophago-gastrectomy offers the best hope. There is the possibility that a combined approach of surgery with pre-operative radiotherapy may lead to an enhanced survival rate.

Extensive tumours that are unsuitable for radical surgery or for intensive radiotherapy are treated palliatively, occasionally by bypass surgery, but more often by intubation. This allows liquids to be taken and is effective in relieving the patient of that most distressing problem—the inability to swallow saliva.

Gastrostomy as a palliative measure offers no relief to the patient, fails to prolong his survival and is therefore not advisable.

DISEASES OF THE STOMACH AND DUODENUM

Peptic Ulcer

In the western hemisphere, peptic ulcer is one of the commonest diseases of the alimentary tract. It affects particularly the working years of a patient's life and its social implications are therefore considerable.

Aetiology. The term 'peptic ulcer' refers to an ulcer found in the lower end of the oesophagus, the stomach, the duodenum, in the small intestine after surgical anastomosis to the stomach, or rarely at the junction of a Meckel's diverticulum with the small intestine. Although the immediate cause of peptic ulceration is digestion of the mucosa by acid and pepsin of the gastric juice, the sequence of events that leads to the development of the ulcer are unknown. Digestion by acid-pepsin cannot be the only factor involved, since ulcers do not develop in some normal people who secrete acid and pepsin in substantial amounts. The problem is aptly stated in the question, 'Why does the stomach not digest itself?' The answer must be that the normal stomach is capable of resisting digestion by its own secretions, so that the problem of ulcer aetiology may be written:

Acid plus Pepsin versus Mucosal Resistance

Theoretically, peptic ulceration may result if gastric secretion is increased on the one hand, or if the resistance of the mucosa is reduced on the other; it is convenient to consider the factors believed to be involved in the development of chronic peptic ulcers according to how they may alter either side of the balance.

1. GASTRIC HYPERSECRETION. The evidence that ulcers occur only in the presence of acid and pepsin is very strong. Peptic ulceration has never been found in patients with pernicious anaemia, and it is very doubtful if a benign chronic ulcer ever occurs in association with achlorhydria. On the other hand, severe intractable peptic ulcer occurs in patients with the Zollinger Ellison syndrome (p. 470), which is characterised by very high rates of gastric secretion. Moreover, patients with duodenal ulcer considered as a group secrete about twice as much acid as do normal individuals, and the duodenal ulcer heals when gastric hypersecretion is reduced by vagotomy. However, gastric hypersecretion does not occur in all patients with duodenal ulcer.

It is in patients with gastric ulcer that factors influencing mucosal resistance must be considered:

2. MUCUS AND CELLULAR TURNOVER (p. 431). Alkaline mucus is the first line of defence for the gastric mucosa, and it may act simply as a protective barrier. Moreover, the superficial layer of the gastric mucosa renews itself every two or three days, so that minor breaks in the mucosa are rapidly healed under normal circumstances. Alteration in the rate of cell renewal in the upper alimentary mucosa may account for the progression of ulcers from acute to chronic.

3. INFLAMMATORY CHANGE. Gastritis, which may be both extensive and severe, commonly occurs in patients with gastric ulcer and, although there is no certain evidence, it seems likely that the gastritis in fact precedes the development of the ulcer; if so, the inflammatory change may well predispose to the development of ulceration by altering the resistance of the mucosa to digestion.

4. BILE REFLUX. Reflux of bile and other secretions into the stomach occurs more frequently in patients with gastric ulcers than in normal individuals or in patients with duodenal ulcers, due presumably to an abnormal pyloric sphincter. Whatever the mechanism, the increased concentration of bile salts in the stomach interferes with the integrity of the gastric mucosa, thus predisposing to the development of ulceration.

5. BLOOD SUPPLY. One of the classical theories of ulcer formation is that the resistance of the mucosa to digestion is reduced as a result of impaired blood supply; such impairment could occur as a result of venous or arterial thrombosis, or because of 'shunting' of blood within the mucosa. Although it is unlikely that this is the cause of all peptic ulceration, it may account for the 'giant' ulcers that occur in the elderly.

Apart from these local mechanisms, several general or constitutional factors are known to be associated with the development of peptic ulcer.

6. HEREDITY. There is no doubt that peptic ulcer tends to occur in families, and the tendency tends to run true to type, so that the children of parents with duodenal ulcer develop duodenal ulcer, and likewise for gastric ulcer. A strong family history is frequently found in patients who develop ulcer in childhood or adolescence.

There is an association between duodenal ulcer and blood group O.

7. SEX INCIDENCE. There are obvious differences both in the incidence and behaviour of peptic ulcer. Duodenal ulcer occurs 5 to 10 times more often in men than in women, and perforation occurs 20 times more often in men. Although these effects may be due to differences in the life pattern of men and women, there are grounds for supposing that the female sex hormones in some way protect against peptic ulcer. Women appear to be particularly protected against ulceration during pregnancy, when active ulcers are virtually unknown; ulcer symptoms which remit during pregnancy commonly recur soon afterwards. The incidence of ulcer symptoms and ulcer complications increase sharply in women at about the menopause. The sex difference in the incidence and behaviour of gastric ulcer is much less than for duodenal ulcer.

8. ENVIRONMENTAL FACTORS. There are marked variations in the incidence of gastric and duodenal ulcer between different countries, and even between different parts of the same country—for example, the proportion of duodenal ulcer to gastric ulcer is very much higher in Scotland than it is in London. There are also differences in the incidence of ulcer as between social classes so that duodenal ulcers tend to be evenly distributed throughout the entire population, while gastric ulcer occurs more commonly amongst poor people, especially in Britain.

9. STRESS. There is an undoubted association between the development of acute ulcers in the stomach or duodenum and physical or mental trauma or surgical operations; similarly there is little doubt that acute anxiety is a

significant factor in precipitating ulcer recurrences and sometimes ulcer complications such as haemorrhage or perforation. Although these effects are presumably mediated via the central nervous system, how stress or anxiety influence the occurrence or behaviour of peptic ulcer is not known.

10. SEASONAL FACTOR. There are strong seasonal factors which can be shown to influence the incidence of ulcer symptoms and mortality rates; in Britain, ulcer mortality is at its lowest in August and September and begins to rise in October, with a further exacerbation of ulcer symptoms in the Spring. The cause of these seasonal variations is unknown.

11. OTHER FACTORS. The incidence of peptic ulceration appears to be increased in patients with chronic lung disease, chronic liver diseases and hyperparathyroidism; similarly, anti-inflammatory drugs such as the salicylates, phenylbutazone and indomethacin have all been associated with an increased incidence of peptic ulcer, especially of gastric ulcer. Corticosteroids are also believed to cause peptic ulcer.

Pathology. Ulcers occurring in the stomach and duodenum may be acute or chronic, the difference being that a chronic ulcer penetrates the muscularis mucosae, whereas an acute ulcer or an erosion does not. Chronic ulcers occur with remarkable regularity in certain sites: in the stomach on the lesser curvature just above the angulus or less frequently at or near the pylorus, while duodenal ulcers occur within 1 cm of the pylorus on the anterior or posterior wall. Acute lesions are frequently multiple, and are less regularly distributed. Benign ulcers occur only rarely on the greater curvature or on the anterior wall of the stomach.

Clinical Features. While there are good grounds for believing that gastric and duodenal ulcers are different diseases with different aetiology and natural history, it is convenient to describe the general features of 'peptic ulcer' as inclusive of both, noting differences where they occur.

Peptic ulcer may present in different ways. The commonest presentation is of chronic, episodic dyspepsia extending over months or years. However, the ulcer may come to attention as an acute episode with bleeding or perforation, with little or no previous history. Occasionally the patient presents with the symptoms of gastric outlet obstruction, having had negligible dyspepsia previously.

PAIN. This is the characteristic symptom of peptic ulcer, and it has three notable features—sharp localisation to the epigastrium, relationship to food, and periodicity. Ulcer pain is typically referred to the epigastrium, in the midline or to the right; wherever it occurs, it is usually sharply localised so that the patient can point to the site. This feature of ulcer pain is so striking as to be called 'the pointing sign'. Occasionally ulcer pain is not clearly localised; it may be referred diffusely in the epigastrium, the lower chest or to the back in the interscapular region in the fifth to eighth thoracic segments. Pain referred to the interscapular area, especially if it is a new feature, suggests the possibility that the ulcer has penetrated posteriorly, involving structures such as the pancreas. The description of the pain is not especially helpful, although patients commonly describe it as gnawing or burning. Pain varies considerably in severity, and it is sometimes helpful to ask the patient to qualify the symptom as 'pain' or as 'discomfort' as a measure of its intensity.

Most patients recognise a relationship of the pain to food, although the relationship varies between patients, and in the same patient from time to time. Duodenal ulcer pain tends to occur between meal times, so that the patient may describe it as 'hunger' pain, which is characteristically relieved by food. A notable feature of duodenal ulcer is pain awakening the patient from sleep between 2 and 4 a.m. The pain of gastric ulcer occurs less regularly; it frequently occurs within an hour of eating, is less often relieved by food, and it rarely occurs at night. Besides the characteristic relief obtained after eating, ulcer pain is almost invariably relieved by antacids, by vomiting and by bed rest in hospital.

Ulcer pain is characteristically episodic occurring regularly each day for days or weeks at a time, then disappearing, to recur weeks or months later. Between attacks, the patient feels perfectly well, and may eat and drink with impunity. Bouts of pain may at first last only a day or so at a time, and occur only once or twice a year. As the natural history evolves, however, episodes begin to last longer and occur more frequently, so that in severe cases remissions of pain may be short-lived and pain or discomfort becomes more or less persistent. The cause for these relapses is difficult to establish. Seasonal factors may be operative, sometimes psychological stress may be blamed, sometimes dietary indiscretion, and sometimes alcoholic excess. Most commonly, no reason can be found for the relapse.

Pain is sometimes absent or so slight as to be dismissed by the patient. Such individuals may complain of other symptoms such as a feeling of 'distension' in the epigastrium or a poorly defined sense of unease after eating. Other complaints include episodic nausea and sometimes anorexia, as well as heartburn or waterbrash. Nausea, anorexia, vomiting and weight loss occur more frequently in gastric ulcer than in duodenal ulcer. Vomiting in ulcer patients almost always relieves pain and when it is persistent may result in weight loss. This helps to distinguish it from vomiting of psychological origin, in which weight is usually maintained. Persistent vomiting in an ulcer subject usually indicates some degree of gastric outflow obstruction, whether due to spasm or organic narrowing of the gastric outlet. In such patients, vomiting is usually copious, so that the patient is 'surprised' at the volume; the patient often recognises food eaten twelve or more hours previously, and he is aware of the unpleasant smell of the vomitus. Although there is no constant change in bowel rhythm during an ulcer relapse, some patients are aware of constipation or diarrhoea when dyspepsia reappears.

PHYSICAL SIGNS. The only physical sign that may be present is 'the pointing sign' by which the patient accurately indicates the site of pain; when accompanied by localised tenderness the sign is practically diagnostic of an ulcer. However, tenderness may be completely absent. In patients with gastric outlet obstruction, the stomach may be visibly distended, a succussion splash may be present, and gastric peristalsis may be seen.

Diagnosis. The diagnosis of peptic ulcer can usually be made from the characteristic history, but it requires confirmation by barium meal examination (Figs 64 and 65) or endoscopy. In some patients the peptic ulcer may present with bleeding, perforation or even pyloric stenosis with few or no previous symptoms. The patient with troublesome dyspepsia, in whom barium meal examination is negative, presents difficulties. Some of these patients will be found to have an ulcer at endoscopy and indeed some may be found to have an early carcinoma. Some clinical judgement has to be exercised in order to distinguish between dyspepsia of psychological origin and that due to organic lesions which have not been detected radiologically. In general, the history in the former is more diffuse, the symptoms rarely as clear cut, the pain poorly localised, and there are no sharply defined tender areas. Positive evidence of a psychological abnormality can usually be obtained. It is a good rule that patients who develop dyspepsia for the first time in middle age should be examined endoscopically if the X-ray is negative. Probably all patients with gastric ulcer should be examined endoscopically since the lesion can be inspected more closely and biopsies taken to exclude a carcinoma. This procedure is also indicated if the physician has any doubt about the nature of the disorder.

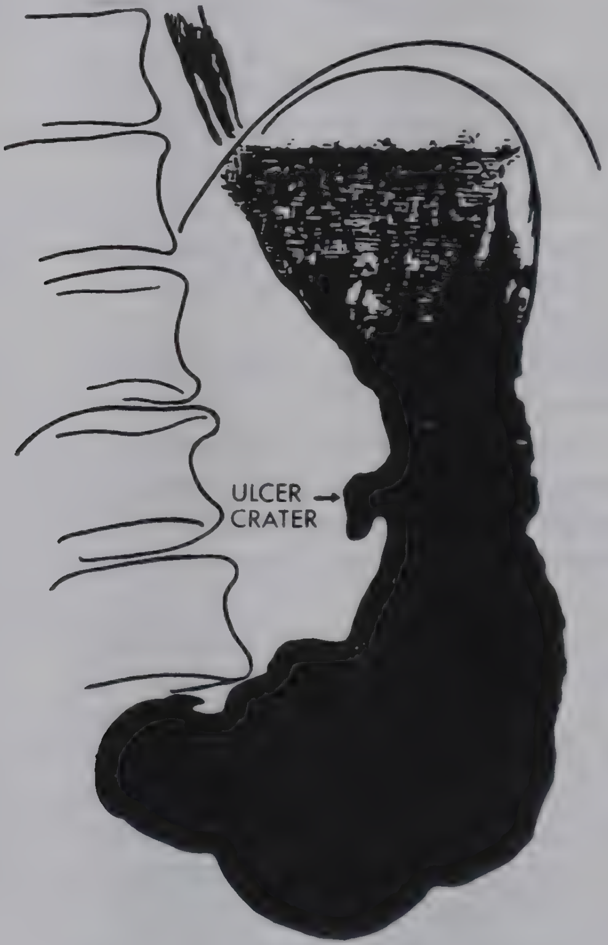


FIG. 64

Stomach following barium meal showing large projection from lesser curvature—gastric ulcer.

GASTRIC SECRETION TEST. Although this test is of limited diagnostic value, a high acid output tends to support the diagnosis of duodenal ulcer and sustains a decision to operate; a low acid output is more consistent with a gastric than a duodenal ulcer.

OCCULT BLOOD. The faeces should be tested for the presence or absence of occult blood in all patients with gastrointestinal symptoms. The test may be carried out on a smear of the stool obtained on rectal examination.

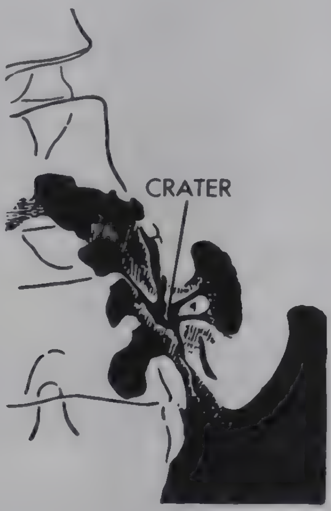


FIG. 65

Oblique view of duodenal cap showing ulcer crater with typical deformity and mucosal folds radiating from the ulcer.

Treatment. There are three objectives in the management of peptic ulcer, namely, the alleviation of symptoms, the healing of the ulcer and the prevention of its recurrence. While there are effective methods for relieving symptoms and for accelerating ulcer healing, at present we have no means of preventing ulcer recurrence nor of altering the natural tendency of ulcer symptoms to remit and relapse. A major problem in interpreting the effectiveness of any particular treatment is the fact that ulcer symptoms do not necessarily reflect ulcer activity. Relief of symptoms can occur in a few days, whereas healing may take weeks. Thus the relief of symptoms, which is naturally the main concern of the patient, does not necessarily mean that the ulcer has healed; some ulcers may persist for many months without any further recurrence of pain, and without any change in size. The more chronic the ulcer, the less chance there is of obtaining healing, because the tissues are distorted by fibrosis. It seems a reasonable aim, therefore, to try to produce ulcer healing in the early stages, in the hope of preventing irreversible changes. Unfortunately this ideal is difficult to attain for economic reasons since the patient is frequently unable to take sufficient time off work, and in any case admission to hospital cannot usually be offered to all patients with an active ulcer, but has to be reserved for patients with complications such as stenosis, bleeding or intractable pain.

REST. The single most effective measure for the relief of ulcer pain and the promotion of healing is bed-rest. This may be undertaken at home under the care of the family doctor or more effectively in hospital; undoubtedly rest in hospital confers additional benefit, possibly because of the release from domestic and business worries. Whatever the reason, pain usually disappears after a few days of bed-rest in hospital.

DIET. It is usually said that a suitable diet for ulcer patients should be mechanically and chemically non-irritating and should consist of small frequent meals. However, there is little experimental evidence to support this advice. It has been shown, for example, that hourly feedings of milk provoke more acid secretion in the stomach than does the ordinary routine of four meals a day, and there is no evidence that the rate of ulcer healing can be accelerated by the traditional bland ulcer diet. Indeed, persistence with such diets may be harmful since they may lead to suboptimal intake of vitamin C. Nevertheless, when symptoms are severe, the patient often appreciates frequent feeds and is helped by dietetic advice along the lines given on page 986.

TOBACCO SMOKING. There is good evidence to show that stopping smoking accelerates the healing of gastric ulcers, and it is likely that this also applies to duodenal ulcers. Thus tobacco smoking should be prohibited.

DRUGS. *Antacids.* Ulcer pain is relieved by antacids. The effectiveness of an antacid is limited by the rate at which it leaves the stomach, so that a dose of an antacid theoretically sufficient to neutralise the gastric acid secreted over many hours in fact does so for less than an hour. Therefore the most effective antacids are those with the quickest neutralising capacity. The preparations commonly used are sodium bicarbonate, magnesium oxide, hydroxide and carbonate, calcium carbonate, bismuth carbonate, aluminium hydroxide and magnesium trisilicate. Sodium bicarbonate is perhaps the most effective of all, but because it can be absorbed it may produce alkalosis; however, this rarely occurs except with excessive dosage, or with vomiting, or when renal disease is present. Accordingly, non-absorbable antacids are usually prescribed, although they do not give such rapid relief because of their slower rate of neutralisation. Calcium carbonate leads to constipation and hypercalcaemia, and magnesium compounds cause diarrhoea. If antacids are given in adequate amounts sufficiently frequently, the pH of the stomach may be raised to a level at which peptic digestion is prevented—above pH 5. Theoretically, the amount of antacid required to achieve this end can be predicted from the secretory capacity of the stomach; the dose is relatively enormous, and it has never been shown that such heroic treatment is essential to ulcer healing, or indeed hastens it. However, when pain is severe, antacids should be given frequently, e.g. 1-2 grammes of pulv. mag. trisil. co. B.P.C. hourly or two-hourly. For the ambulant patient, antacid preparations in tablet form are more convenient (Gelusil, Nulacin); they may be carried in the pocket, and chewed or sucked whenever pain occurs. The diarrhoea caused by magnesium salts and the constipation produced by calcium salts or aluminium hydroxide can be prevented by a suitable mixture of the two groups of antacids, the exact proportions depending on the individual patient.

Anticholinergics. Drugs of the anticholinergic group inhibit vagal stimulation, thereby reducing gastric secretion and motility. All drugs of this class exert a general anticholinergic effect, so that salivary secretion is reduced, intraocular pressure is raised, and urinary retention may occur. Many such drugs have been synthesised with the object of increasing the desired effect on the stomach and of reducing these undesirable side-effects, but there is no good evidence that any one preparation is better than another in this respect. Of the drugs available, propantheline (15 mg) and poldine methylsulphate (2-6 mg) are perhaps best. The dose is that which just avoids side-effects; the drug is taken three or four times a day and the amount is gradually increased until tolerance is established. Doubling the dose to be taken at night is useful in preventing the occurrence of nocturnal pain. Large doses of anticholinergics cannot be tolerated by ambulant patients because of the blurring of vision; they are not well-tolerated by the elderly, and they are positively contraindicated in patients with glaucoma, prostatism or gastric retention.

Liquorice Derivatives. It has been shown that two pharmacological preparations derived from liquorice, carbenoxolone sodium and deglycyrrhizinated liquorice, accelerate the healing of gastric ulcers in ambulant patients. The mechanism of action of these drugs is unknown; the evidence that either exerts beneficial effects on duodenal ulcer is not convincing. Carbenoxolone may cause sodium and water retention, potassium depletion and hypertension; these side-effects are an indication for terminating treatment with carbenoxolone. It should be prescribed only when the patient can be properly supervised and is contraindicated when the patient is elderly or where there is hypertension or a previous history of heart failure. Deglycyrrhizinated liquorice is claimed to have the same healing properties without the undesirable side-effects of carbenoxolone.

Tranquillisers. Psychological stress may precipitate a relapse of ulcer symptoms, and ulcer symptoms in turn may lead to further anxiety. Thus tranquillisers may have a real if limited place in the treatment of ulcer subjects. Drugs such as phenobarbitone or diazepam are useful in controlling anxiety when it is present, or as an adjunct to bed-rest when this becomes necessary.

SURGICAL TREATMENT. Modern surgical treatment has much to offer the patient with intractable peptic ulceration. It can relieve severe or persistent symptoms and prevent complications. While in many cases the assessment of the patient's disability is straightforward, in patients in whom anxiety, depression or other affective disorder is present, the decision becomes difficult even for the experienced gastroenterologist. Elective surgery should be considered in the following circumstances:

1. When an ulcer has failed to heal, and symptoms persist or recur so as to interfere with the enjoyment of life, or reduce the capacity to work. The indications for surgery are strengthened if the ulcer has developed in adolescence or young adult life, if there is a strong family history, or if there has been a previous complication such as haemorrhage or perforation.

2. When there is an ulcer which has produced gastric outlet obstruction, or an hour-glass stomach because of fibrosis.

3. When there is a gastric ulcer the nature of which is uncertain or which has failed to heal in three months.
4. In a recurrent ulcer following previous gastric surgery.

There is no single, ideal surgical operation suitable for all ulcers and all patients. For a gastric ulcer, the operation of choice is partial gastrectomy preferably with a Billroth I anastomosis, in which the ulcer itself and the ulcer-bearing area of the stomach is resected. For duodenal ulcer the acid secretory capacity of the stomach may be reduced by gastrectomy, either partial or distal (antrectomy), or by vagotomy which eliminates nervous stimulation of gastric secretion (Fig. 66). A vagotomy is usually truncal, which means that the complete nerve trunks are divided. After truncal vagotomy, gastric emptying may be retarded, so that vagal section has to be combined with a drainage procedure such as pyloroplasty or gastroenterostomy. Vagotomy is preferred to partial gastrectomy because of the lesser mortality and lower incidence of long-term complications. The choice of operation may be guided to some extent by measurement of the secretory capacity of the stomach. When the acid output is very high, some surgeons prefer to combine antrectomy with vagotomy in order to ensure that gastric secretion is sufficiently reduced. At the other end of the scale, gastrojejunostomy alone without vagotomy may be considered in patients with a low acid output.

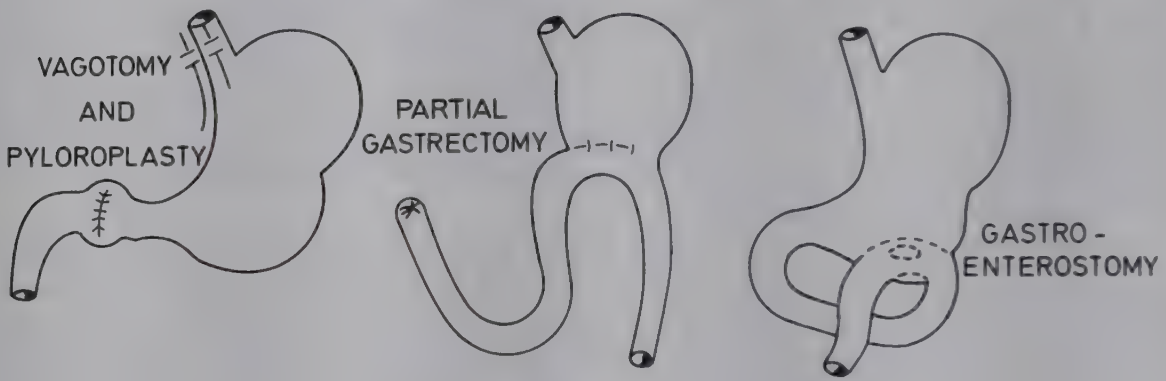


FIG. 66

Operations for duodenal ulceration

It should be re-emphasised that relief of symptoms is the commonest objective in elective surgery for a peptic ulcer and while it is important that the patient should not be over-persuaded to accept operation, it must also be remembered that much unnecessary suffering can be imposed on patients by denying surgery in the face of medical failure.

Complications. The common complications of peptic ulcer are haemorrhage, perforation and obstruction. Ulcer-cancer is discussed under carcinoma.

Gastroduodenal Haemorrhage

Bleeding as judged by a positive test for occult blood in the stools can be detected at some time or another in most cases of peptic ulcer. Gastroduodenal haemorrhage as a complication is taken to mean bleeding of sufficient severity as to cause symptoms on its own account. It is a serious complication of peptic ulcer, carrying a mortality of the order of 10 per cent, so that all patients with a history of significant blood loss within the previous 48 hours should be admitted to hospital.

Aetiology. The common causes are, (1) chronic duodenal ulcer, (2) 'acute' gastric ulcer or gastric erosions, (3) chronic gastric ulcer, (4) carcinoma of the stomach, and (5) portal hypertension causing oesophageal varices. In Britain the first three account for about 90 per cent of the cases.

Acute ulcers range from minute erosions to shallow ulcers about 2-4 cm in diameter and involving only the mucosa; erosions may occur singly, in small groups, or in severe cases may be so numerous as to be virtually confluent causing an acute erosive gastritis. They are difficult to demonstrate radiologically; a positive diagnosis requires direct inspection by endoscopy. Salicylates are the commonest cause of haematemesis associated with acute erosions, the majority of patients giving a history of aspirin ingestion within the previous 48 hours. In some cases the erosions are related to the consumption of alcohol or a combination of alcohol and aspirin; other causes include drugs such as phenylbutazone, systemic infection, stress (especially post-operative) and intra-cerebral lesions. Bleeding from oesophageal varices secondary to portal hypertension can be extremely severe and demands special measures for its management. It is a relatively infrequent cause of haematemesis in Britain, though it occurs more frequently in the United States; even in those patients, however, bleeding may be due to an associated acute or chronic ulcer, rather than from the varices. Bleeding from peptic oesophagitis is usually mild.

Clinical Features. Haemorrhage manifests itself by the vomiting of blood (i.e. haematemesis) or by the passage of altered blood in the stools (i.e. melaena). A frank haematemesis indicates a large bleed, usually involving a loss of about 25 per cent of the blood volume. If the blood has been in the stomach for any length of time, it becomes partially digested and appears brown and granular in the vomit—so-called 'coffee grounds'. Blood passing through the intestinal canal is also altered in appearance, so that the stool becomes black and sticky; however, in severe bleeding, transit through the intestine may be so rapid that the blood passed per rectum may be little altered in appearance. Since rapid bleeding is more likely to induce vomiting, the prognosis is worse with a haematemesis than with a melaena. Apart from the rate of blood loss, the outlook in gastroduodenal haemorrhage depends also on whether the bleeding stops spontaneously, and this in turn depends on the type of vessel involved. If the bleeding is from a large artery, or a sclerotic vessel which cannot retract, the chance of cessation is slight; if bleeding is capillary and the vessels can retract, bleeding will cease spontaneously. It follows that bleeding from a chronic ulcer in which large vessels may be involved is likely to be more severe than that from a single or several acute erosions. Equally, severe bleeding in itself suggests that a large vessel is involved and the outlook therefore more grave. The outlook is greatly influenced by the age of the patient, mortality increasing steeply after middle age; bleeding from the upper alimentary tract in a patient over the age of 45 should be regarded as a serious emergency irrespective of the state of the patient when first seen.

Whatever the cause of the bleeding the patient complains of weakness, and faintness sometimes amounting to syncope, nausea or sweating; these symptoms are followed by the actual vomiting or passage of blood.

On examination, the patient is pale, sweating and anxious. He may be restless or disorientated because of cerebral anoxia. Depending on the physiological response to the haemorrhage, the pulse rate will be raised and the blood pressure may show a fall. These signs may be absent in the young patient in whom compensatory mechanisms are more effective.

The haemoglobin level will not alter until haemodilution occurs, and this may not take place for some hours, nor be complete for some days. There is no simple laboratory procedure which will give a reliable estimate of the amount of blood loss until haemodilution is complete, so that in ordinary circumstances the assessment of the degree or rate of bleeding depends on clinical judgement: serial recording of the pulse rate and blood pressure gives the most useful and simple objective measure available.

Treatment. The patient should be put to bed, and blood taken for haemoglobin estimation, packed cell volume and blood grouping. A half-hourly chart of blood pressure and pulse rate is begun. An intravenous drip must be set up in case further haemorrhage occurs, and a naso-gastric tube should be passed into the stomach. The patient is usually restless and anxious, but this may be due as much to cerebral anoxia as it is to fright. If sedation is required, drugs such as diazepam or phenobarbitone are to be preferred to morphine because of its emetic effects. A blood transfusion should be given if the pulse rate is faster than 100 per minute or the systolic pressure lower than 100 mm Hg. In addition a haemoglobin level of less than 10 g/100 ml on admission, even if the patient is not shocked at that stage, is a further indication for transfusion. It is important that every patient is transfused adequately, because cerebral anoxia may lead to restlessness or even delirium, and if it is sufficiently prolonged cerebral thrombosis may develop in the elderly. Similarly, the coronary blood supply may be compromised leading to angina or even myocardial infarction. Prolonged hypotension may result in acute renal failure and permanent renal damage. A further indication for transfusion is the patient who is likely to require surgical treatment to arrest the haemorrhage. The danger from over-transfusion is heart failure; in the elderly, especially in those presenting with a severe bleeding or those likely to have continued bleeding, the safest guide is measurement of the central venous pressure by passing a catheter into the subclavian vein. Rise in pressure indicates right ventricular failure from excessive transfusion whereas a fall is an indication of continuing or recurrent haemorrhage. When it is not possible to introduce this ‘central line’, the jugular venous pressure should be repeatedly checked. The hourly or half-hourly aspiration of stomach contents by means of the naso-gastric tube is also useful in detecting further bleeding.

The next step in management is to decide the further investigation of the patient in consultation with a surgical colleague. The importance of early consultation with a surgeon cannot be over-emphasised; although the immediate situation may not give rise to anxiety, the surgeon should see the patient at the earliest opportunity in case there is recurrent haemorrhage. The cause of the bleeding should be established as soon as possible by means of urgent radiological or endoscopic examination. A possible limitation to the former is the presence of blood clots in the stomach which may conceal a crater, and acute erosions may not be demonstrated. The presence of blood in the stomach is a lesser disadvantage in endoscopic examination. Subsequent management is determined largely by the age of the patient, the severity of the haemorrhage, the site or cause of the bleeding, and recurrent bleeding. There are no absolute criteria governing the decision to operate, and again each case has to be considered on its merits. As a general rule emergency surgery should be advised in any patient over 50 who has had severe bleeding, or is known to have a chronic ulcer, or who bleeds again after admission. On the other hand, if the patient can be shown to be bleeding from acute erosions, medical therapy can be continued much longer.

Opinions differ as to the choice of operation. In general, partial gastrectomy is the operation of choice for a chronic gastric ulcer, whereas in duodenal ulcer the lesion may be exposed by an incision at the pylorus, occluded by sutures and a pyloroplasty and vagotomy performed.

Prognosis. The prognosis in gastroduodenal haemorrhage is related to the patient's age, the causative lesion and the severity of the initial bleeding. It is a serious condition and approximately 10 per cent of patients admitted to hospital as an emergency will die. Patients with a chronic ulcer are likely to bleed again months or years later; in such patients, elective surgery for the ulcer should be considered, after they have recovered from the initial bleed.

Acute Perforation of a Peptic Ulcer

When free perforation occurs, the contents of the stomach escape into the peritoneal cavity. If perforation occurs without loss of contents, as in the accidental perforation of the empty stomach at gastroscopy, few symptoms are produced and the accident may even pass unnoticed. It follows that the symptoms of perforation are those of peritonitis, and they are in proportion to the extent of peritoneal soiling. Occasionally the symptoms of perforation appear and rapidly subside; presumably the perforation has then closed spontaneously, or more commonly the ulcer has perforated locally into an area confined by adhesions to adjacent structures. Perforation occurs more commonly in duodenal than in gastric ulcers, and usually in ulcers on the anterior wall.

Clinical Features. Although perforation may occur as the first sign of ulcer, usually there is a history of dyspepsia. The most striking symptom is sudden, severe pain, the onset of which may be so incisive that the patient can time it to a minute. The pain is usually intense, and its distribution follows the spread of the gastric contents over the peritoneum. Thus, initially the pain may be referred to the upper abdomen, but very quickly it becomes generalised; shoulder tip pain may occur as a result of irritation of the diaphragm. The pain is accompanied by the signs of shock and shallow respiration due to limitation of diaphragmatic movements. The abdomen is held immobile, and there is generalised board-like rigidity; intestinal sounds are absent, and liver dullness to percussion decreases due to the presence of gas under the diaphragm. Vomiting is common. After some hours, the symptoms improve, though the abdominal rigidity remains. This period of improvement may deceive the clinician examining the patient for the first time; after this temporary improvement, manifestations of general peritonitis follow the initial peritoneal irritation and the patient's condition deteriorates.

Differential Diagnosis. The all important issue is to decide whether the patient requires laparotomy. All the causes of the 'acute abdomen' or those which simulate it must be considered (p. 500). A plain film of the abdomen in the erect position will help to settle the diagnosis, since free gas within the peritoneal cavity, if in sufficient amount, will show as a translucent crescent between the liver and diaphragm.

Treatment. After initial treatment of the patient for shock, the acute perforation should be treated surgically either by simple closure, or occasionally in the case of perforation of a chronic ulcer by partial gastrectomy, or closure combined with vagotomy and drainage. More than half the patients who have a simple closure will eventually require a further elective operation for recurrence of ulcer symptoms, and for this reason some surgeons recommend a definitive procedure for the ulcer at the time of operation.

Prognosis. Acute perforation carries a mortality of about 5 per cent, but the outlook depends on the degree of peritoneal soiling, and therefore on the size of the perforation and the amount of stomach contents released into the peritoneum. The time interval elapsing between the onset of perforation and the time of operation also determines the outcome—the longer the delay, the greater the risk of death from peritonitis.

Gastric Outlet Obstruction

(PYLORIC STENOSIS)

A complication of an ulcer in the region of the pylorus is gastric outlet obstruction due to constriction from fibrosis. The obstruction may be due to actual organic narrowing from scar tissue, or to oedema or spasm produced by the ulcer; frequently it is a combination of all three. Long-standing obstruction may lead to severe 'retention' gastritis, or even to secondary gastric ulcer.

In addition to chronic duodenal ulcer, or benign gastric ulcer at or near the pylorus, gastric outlet obstruction may be caused by carcinoma of the antrum and by a rare condition known as adult hypertrophic pyloric stenosis. The syndrome of gastric outlet obstruction is loosely described as 'pyloric stenosis', even when the cause is chronic duodenal ulcer, and the stenosis is distal to the pylorus; thus in 'pyloric' obstruction due to duodenal stenosis, the pylorus itself may be seen radiologically to be greatly dilated.

Clinical Features. Most commonly the condition is due to a chronic duodenal ulcer, so that there will be a preceding history of dyspepsia. When there is no such history, a patient with gastric outlet obstruction is likely to have a pyloric carcinoma. When there has been an ulcer, the symptoms of dyspepsia change, so that vomiting becomes a prominent feature, and nausea replaces normal appetite. Vomiting produces such striking relief that a patient may even start to eat or prepare food immediately after the stomach has been emptied. If the obstruction progresses, the stomach dilates and accommodates large volumes so that eventually surprisingly large amounts of gastric content may be vomited. Articles of food which have been eaten 24 hours previously may be recognised in the vomit. An earlier symptom is a sense of repletion soon after eating: the patient feels satisfied and full up after taking a relatively small amount of food. The vomitus of pyloric obstruction is characteristically foul-smelling and free of bile. The loss of gastric contents results in water and electrolyte depletion. If large amounts of hydrochloric acid are lost, as occurs particularly in obstruction due to duodenal ulcer, alkalosis develops.

Physical examination shows evidence of wasting and dehydration, and there may be signs of tetany (p. 652). Splashing may be elicited in the stomach four hours or more after the last meal or drink, and sometimes the patient is aware of it himself. In normal persons splashing occurs for less than an hour after meals because gastric emptying is rapid. Visible gastric peristalsis is the sign of greatest value in pyloric obstruction and the abdomen should be inspected for its presence. If the patient takes a fluid diet with large amounts of milk, the signs of obstruction may be masked and nutrition may be maintained, even resulting in obesity.

Diagnosis. The diagnosis is made on the history and physical findings, and can be confirmed by *aspiration of the stomach*. A volume in excess of 100 ml after fasting or 200 ml four hours after a meal is suggestive; if the aspirate contains food residue, or is foul, the diagnosis is certain. However, a fine bore nasogastric tube may become blocked by debris, giving a false impression of normality; if in doubt a wide bore stomach tube should be used.

The radiological signs are (1) an increase in the fasting residue of the stomach, (2) dilatation of the stomach with or without excessive peristalsis, (3) a lesion at or near the pylorus, and (4) delayed gastric emptying. If a large gastric residue persists after several days treatment, further barium meal examination is unlikely to be helpful and the patient should be prepared for surgery.

Laboratory Tests. An estimation of the blood urea and serum electrolytes should always be carried out. In severe stenosis, the blood urea will be raised because of dehydration and the patient will be alkalotic because of loss of hydrogen ions from the stomach.

Treatment. The most urgent requirements are to correct dehydration and to restore electrolyte balance, usually by intravenous fluid. The stomach should be aspirated morning and evening to restore its tone; the volume removed may be replaced by half as much of a solution of isotonic saline containing 2 g KCl/*l*. In severe cases only liquids are allowed by mouth; where obstruction is not severe a homogenised diet may be given. A multi-vitamin preparation should be given by injection to all but the mildest cases.

The majority of patients will be greatly improved by these methods; the volume of the gastric aspirate steadily declines, and emptying of the stomach returns to near normal. It is then necessary to consider the timing of an operation such as gastroenterostomy or gastrectomy. Operation should not be too long deferred. If obstruction persists, with no improvement after five to seven days, nothing is gained by procrastination, and indeed the patient may deteriorate because of electrolyte imbalance. Relief of obstruction by medical means should be seen as an opportunity to complete investigation and to render the patient as fit as possible for subsequent elective surgery.

Zollinger Ellison Syndrome

This is a rare disorder in which severe peptic ulceration and marked gastric hypersecretion are associated with a tumour of the islets of the pancreas. The tumour cells secrete large amounts of the hormone gastrin into the circulation; this in turn stimulates the parietal cells excessively, resulting in hypersecretion. The acid output of the stomach may be so great that the 'acid tide' may reach the upper small intestine, reducing the luminal pH to 2 or less; at this pH pancreatic lipase is inactivated and bile salts may be precipitated, resulting in diarrhoea and steatorrhoea. Excessive gastric secretion is almost invariable, giving large volumes on aspiration under 'basal' conditions. A characteristic feature is that the administration of an exogenous stimulus such as histamine or pentagastrin does not increase the secretory rate much above resting or 'basal' values, since the stomach is already continuously secreting at or near maximal rates because of the high levels of endogenous gastrin in the circulation.

The ulcers are often very large and may occur in unusual sites such as the jejunum or the oesophagus. The history is usually short and bleeding and perforation are common. The syndrome may present in the form of severe recurrent ulceration following a standard operation for peptic ulcer, the underlying cause not having been recognised at the time of the operation.

The diagnosis should be suspected in all patients with unusual or severe peptic ulceration, especially if the barium meal examination shows abnormally coarse gastric mucosal folds, and may be confirmed by finding very high levels of gastrin in the circulation. Medical treatment is ineffective. Theoretically the condition should be cured by removing the pancreatic tumour, but this is not usually possible because of its diffuse nature or the presence of metastases. In these circumstances, a total gastrectomy is the treatment of choice, since any procedure which leaves functioning parietal cells in the stomach will lead to recurrent ulceration.

Complications following Operations on the Stomach

Although most operations carried out for the relief of peptic ulcer are successful, 10 per cent of patients will develop complications months or years afterwards. Some of these complications such as anaemia and nutritional impairment develop insidiously, so that patients who have had an operation on the stomach should be seen at least once yearly for review. Only the late complications of gastric operation are considered here.

Recurrent Ulcer

As a general rule, recurrence of ulceration after surgery for duodenal ulcer implies failure to reduce the secretory capacity of the stomach to a level which is safe. A *jejunal ulcer* may develop, just distal to the jejuno-gastric anastomosis after partial gastrectomy or after gastroenterostomy; since the jejunal mucosa is more susceptible to acid-pepsin digestion than the mucosa of the stomach or duodenum, the level of acid secretion at which jejunal ulceration may develop is lower than that found in unoperated duodenal ulcer. After incomplete vagotomy, a jejunal ulcer may occur if the vagotomy has been combined with a gastroenterostomy, or the original duodenal ulcer may recur if the vagotomy has been combined with pyloroplasty.

Clinical Features and Diagnosis. After months or years of freedom following the operation, ulcer pain recurs. The symptoms are much the same as they were prior to operation; in the case of a jejunal ulcer the relationship to food is not so clear cut and pain may be referred to the midline or to the left. Occasionally a jejunal ulcer will come to light because of a melaena or unexplained anaemia of recent onset, or more rarely because of a perforation. Recurrent ulcers of the jejunum and duodenum are difficult to demonstrate by X-ray examination. In the case of a jejunal ulcer, only 'jejunitis' or coarsening of the jejunal mucosa may be seen instead of an ulcer niche. It may be impossible to distinguish a recurrent duodenal ulcer from the deformity that is inevitably produced by pyloroplasty. In both instances, however, it may be possible to see the ulcer at endoscopy. Gastric secretion tests are helpful, since it is unusual to find a jejunal ulcer where the maximal acid output is less than 15 mEq/hour. After vagotomy an insulin test will show whether or not vagal section has been complete.

A rare but very serious complication of a jejunal ulcer is a *gastrojejunocolic fistula*, due to perforation of the jejunal ulcer into the colon. Flow is from colon to jejunum, and this leads to bacterial contamination of the upper intestine with resultant diarrhoea, malabsorption and consequent weight loss. Because of the direction of flow, the fistula is best demonstrated by a barium enema examination. The clinical condition of the patient may deteriorate very rapidly, so that urgent operation is often necessary.

Treatment. In general, the symptoms of jejunal or recurrent duodenal ulceration cannot be controlled by medical treatment; for this reason, and because of the enhanced risk of bleeding or perforation, further surgery is usually advised. When ulcer recurrence is due to an incomplete vagotomy, unless a major nerve trunk is found at laparotomy, an antrectomy or limited gastrectomy is the wisest procedure; in the case of a jejunal ulcer occurring after partial gastrectomy, a vagotomy is indicated rather than revision of the gastrectomy alone.

Suture Ulcer

Jejunal ulcer is to be distinguished from an ulcer which appears on the anastomosis. The latter is due to the presence of non-absorbable sutures such as silk which erode into the lumen and can be seen as knots or lengths of material on gastroscopy. Unlike jejunal ulcers, suture ulcers are not necessarily associated with high acid outputs; however, they are similarly unresponsive to medical management, and usually require further operation in the form of a local resection and reconstruction of the anastomosis.

Recurrent Gastric Ulcer

An ulcer in the body of the stomach away from the anastomosis may also occur. This usually develops in association with gastric stasis, and surgical relief of the obstruction may be required to attain healing.

Biliary Gastritis

This results from a reflux of bile into the stomach. On endoscopy the mucosa is often red and bleeding. The patient complains of loss of appetite, nausea and epigastric discomfort sometimes brought on by eating, hot drinks or the taking of alcohol. The physician may suspect the development of carcinoma. Patients are reassured that they have not developed another ulcer. They are advised to stop smoking and drinking alcohol and to take frequent small dry meals. Additional measures include metoclopromide monohydrochloride, 10 mg q.i.d. before meals, and broad spectrum antibiotics may be given if there is evidence that the stomach is colonised by excessive numbers of bacteria. Revisional surgery may be required when these measures fail and especially if there is any suggestion of a mechanical cause for bile reflux into the stomach.

Post-Cibal Syndromes

After any operation on the stomach, a number of patients will complain of symptoms after eating a meal and these may be classified as follows:

1. **The Small Stomach Syndrome.** About 50 per cent of patients feel distended and uncomfortable during and after a meal. After gastrectomy, the belief is that the remnant cannot readily accommodate the volume of the meal; but the same symptom may occur after vagotomy and drainage when interference with the mechanisms regulating accommodation-relaxation of the intact stomach is presumed to be responsible. Although these symptoms tend to lessen with time, a few patients restrict their food intake more or less permanently because of these symptoms and this, rather than malabsorption, may account for their failure to gain weight.

2. **Food Intolerance.** Approximately 5 per cent of patients find that they are no longer able to eat such foods as eggs, milk or tomatoes.

3. **Dumping Syndrome.** The symptoms consist of a feeling of intense drowsiness coupled with muscular weakness, and this sensation of asthenia may be

described as 'tiredness' or 'fatigue'; there may be flushing and palpitations in addition. The sensation of weakness may be so intense that the patient finds it necessary to lie down. These symptoms usually develop immediately after a meal, and particularly after hot sweet foods such as milk puddings, and liquids such as cocoa. The pathogenesis of these symptoms is still uncertain, but they are probably related to the rapid emptying of the stomach contents which are 'dumped' into the jejunum. This in turn may produce movement of fluid from the extracellular compartment into the bowel lumen, and to a reduction in plasma volume; these or other factors may cause release of vaso-active substances into the circulation causing peripheral vasodilatation. Whatever the mechanisms, clinical experience shows that this train of symptoms disappears with time in the majority of patients as they become adapted to the stimuli which produce them and learn what foods to avoid.

TREATMENT. The patient should be given an explanation of his symptoms and advised concerning his eating habits. Avoidance of hot fluids like soup or strong sweet tea may prevent attacks. Meals should be of small bulk and eaten dry, and fluids taken between meal times. If it is found that a large meal is the chief offender, it may be eaten at the end of the day when the patient has the opportunity of resting afterwards. Treatment with anticholinergics to delay emptying, or propranolol 20-40 mg before meals to reduce the circulatory symptoms, may be worth a trial. If symptoms are severe and persistent, it may be necessary to advise further surgical treatment, but this should not be considered for at least two years after operation, since symptoms tend to improve with time.

4. **Hypoglycaemia.** Symptoms of weakness, tremor and faintness, associated with a hungry or empty sensation in the epigastrium, may develop between one and two hours after a meal. These symptoms are due to hypoglycaemia: glucose is rapidly absorbed after the operation because of accelerated gastric emptying, causing abnormally high levels of blood glucose, and this in turn leads to excessive secretion of insulin which accounts for the hypoglycaemia (see alimentary glycosuria, p. 686). The diagnosis can be confirmed by estimating the blood sugar during an attack or by giving the patient a glucose tolerance test and noting the appearance of symptoms afterwards. Alternatively, the attacks can be reproduced by giving a small dose of insulin intravenously. Symptoms can be prevented by taking glucose at the appropriate time or, better still, by eating ample amounts of meat or fat at the two main meals. This measure may reduce the emptying rate of the stomach and hence reduce the tendency to hypoglycaemia. Elderly patients who are subject to these attacks may have to be warned of the dangers of driving a car; similarly, patients in dangerous occupations such as steel erecting may have to seek other employment.

Anaemia

Anaemia is a common sequel to operations on the stomach, particularly after partial gastrectomy. It occurs more frequently in women, up to 50 per cent of whom, even after vagotomy, may become anaemic. Anaemia is due to inadequate absorption of iron, or to recurrent minor blood loss from gastritis or oesophagitis. Its incidence increases in the first 10 years and then remains relatively stationary, as the stores of body iron are exhausted. Its occurrence is a measure of the degree of post-operative supervision, because it is preventable by and responds to the administration of iron. Megaloblastic anaemia is comparatively rare and responds promptly to vitamin B_{12}.

Post-operative Diarrhoea

Diarrhoea may occur after any operation on the stomach, but especially after vagotomy. Most patients report some looseness of the stools following vagotomy, but this may be no inconvenience to the patient, and indeed is often welcomed. Moderate or severe diarrhoea occurs in about 10 per cent. This is characteristically episodic, several watery stools being passed daily for several days, to be followed by constipation or by normal bowel habit. A striking feature is the sense of urgency associated with the diarrhoea; defaecation may be precipitate, and the patient becomes worried because of the fear of soiling himself. Treatment is difficult, since the diarrhoea is unpredictable in occurrence. The usual symptomatic measures should be tried, such as codeine and the patient advised to take a substantial dose when diarrhoea occurs. If vagotomy has produced a marked depression of acid secretion, the diarrhoea may be associated with bacterial colonisation in the small intestine; it is then worth trying a short course of tetracycline, 250 mg four times a day for about 10 days, in order to alter the bacterial flora. If there is an associated steatorrhoea which cannot be otherwise corrected, a low fat diet is indicated.

Nutritional Impairment and Osteomalacia

In a proportion of patients there is some nutritional impairment following gastric surgery, the risk of which increases with the extent of any resection. Severe weight loss is its most common manifestation, but there may also be a malabsorption syndrome with steatorrhoea and osteomalacia. The latter may develop for the first time 15 to 20 years after partial gastrectomy, and may present as bone pain or as a pathological fracture. At the present time, osteomalacia is not a recognised complication of vagotomy.

Gastritis

Gastritis signifies an acute or chronic inflammation of the stomach. Our knowledge of the changes that occur in the gastric mucosa has been obtained in three ways: (1) by direct observation of the gastric mucosa in patients with gastrostomies, as in the famous cases of Alexis St Martin observed by Beaumont over a century ago, and the more recent subject Tom; (2) by gastroscopic observation; and (3) by histological examination of specimens removed at operation, biopsy or autopsy.

There is poor agreement between these different approaches, so that the classification of gastritis is difficult. If histological specimens are examined, it is very rare to find a normal stomach completely free from any signs of inflammation. In this sense 'gastritis' is almost an invariable finding in adults. However, there are gross departures from this 'normal' state of affairs, even if they do not give rise to symptoms. For these reasons the condition is best defined in histological terms as *acute* or *chronic* gastritis.

Acute Gastritis

The commonest form of acute inflammation of the gastric mucosa is that caused by the ingestion of irritant materials. Perhaps the most frequent irritant is alcohol; others include drugs such as aspirin and phenylbutazone and strong corrosives. Acute gastritis may also occur during the course of specific infection such as diphtheria or influenza; a particularly severe variety may occur during the course of septicaemia. Bile is also irritant to the stomach and may cause an acute gastritis as a complication of gastric surgery.

Macroscopically, there is engorgement of the mucosa with swelling, patches of adherent mucus and sometimes small erosions. Microscopically, there is hyperaemia, infiltration with inflammatory cells, and desquamation of the superficial layer. In his original observations on Alexis St Martin, Beaumont noticed the considerable degree of inflammation that might occur in the stomach without symptoms. This finding has been repeatedly confirmed, suggesting that the gastric mucosa is a relatively insensitive tissue.

The symptoms associated with acute inflammation of the stomach are anorexia, nausea, epigastric ache and heartburn; since the superficial layers of the gastric mucosa can regenerate within 72 hours, it seems unlikely that a single attack or even several attacks of acute gastritis could lead to permanent histological change in the stomach. Presumably for the same reason, the symptoms of acute gastritis are short-lived.

Diagnosis. Gastritis cannot be diagnosed with certainty by radiological examination. At gastroscopy, the mucosa is reddened and seems swollen, and is easily damaged and friable.

Any inflammatory process is likely to decrease the acid output by depressing the activity of the parietal cells, and also by increasing the secretion of the alkaline non-parietal component. Acid secretion tends to recover after the inflammation has subsided.

Treatment. A patient who has consumed excessive alcohol or irritant foods should obviously cease doing so and then the symptoms will disappear in a few days, though it may be longer before the gastric mucosa returns to normal. Similarly, the gastritis associated with specific fevers disappears as infection subsides. The treatment of biliary gastritis is dealt with on page 472.

Chronic Gastritis

Two stages are recognised, according to the severity of the histological changes. In *chronic superficial gastritis* there is infiltration of the mucosa with plasma cells, eosinophils and neutrophils, and there is some atrophy of the superficial parts of the glands. In *chronic atrophic gastritis* there is more extensive inflammatory cell infiltration, with marked atrophy of the glandular structures, and a great diminution in the specific secretory cells. In many cases the mucosa comes to resemble that of the small intestine, a change that is termed 'intestinal metaplasia'.

Chronic gastritis is found in association with gastric ulcer and gastric carcinoma. It occurs invariably in pernicious anaemia, and also in some patients with thyroiditis and Addison's disease; in these patients it is believed that the atrophic changes are due to an auto-immune process, this concept being supported by histological evidence of lymphocytic and plasma cell infiltration, and the presence of circulating antibodies to the gastric mucosa and to other tissues such as thyroid.

Diagnosis. Severe chronic gastritis may be diagnosed on barium meal examination, because the mucosal folds are smaller than normal and reduced in number or even completely absent as in pernicious anaemia. These appearances may be confirmed at gastroscopy when, in addition, the submucous plexus of veins may be seen through the thin mucosa. These atrophic appearances are constantly present in pernicious anaemia, and they are often seen in localised patches in patients with gastric ulcer and gastric carcinoma. It is very doubtful whether atrophic gastritis can produce gastrointestinal symptoms and its existence is usually suspected only because of an associated anaemia or the finding of diminished or absent secretion of acid or intrinsic factor; the diagnosis can be confirmed by biopsy.

Treatment. No method is at present known for stimulating the mucosa to regenerate.

Carcinoma of the Stomach

Carcinoma of the stomach is one of the commonest malignant tumours of the gastrointestinal tract, although its incidence varies considerably in different parts of the world—for example, the tumour is common in Japan and relatively uncommon in the U.S.A. These variations have been attributed to environmental factors, such as trace elements in water, or differences in methods of food preparation: the incidence of gastric cancer in Japanese immigrants to America is much less than it is in Japan. Patients with pernicious anaemia have a 10 per cent chance of developing gastric cancer and this increased risk may extend to achlorhydria from other causes, including gastric surgery.

Pathology. Almost 70 per cent of all gastric cancers occur at the pylorus or in the antrum; the lesion is sharply limited to the stomach, and does not spread to the duodenum. Such growths may produce symptoms of pyloric obstruction and are important causes of gastric outlet obstruction. Lesions of the body of the stomach often involve the greater curvature and produce a fungating ulcerating mass. Least common is a diffuse infiltrating lesion spreading throughout the body of the stomach and producing the so-called leather-bottle stomach. These are the descriptions of advanced cancer. In the early stages, when the carcinoma is confined to the mucosa, the lesion may be represented only by a depressed area with obliteration or distortion of the mucosal folds, by irregular ulceration on an elevated base, or by a small polypoid lesion. Such lesions can be seen and a biopsy taken during gastroscopy at a stage when the cancer is potentially curable by resection. The tumour is generally an adenocarcinoma and spread occurs by direct extension through the stomach wall, by lymphatic permeation and by embolism via the portal vein to the liver and thence to the systemic blood stream.

ULCER-CANCER. Gastric carcinoma may present as a malignant ulcer, and whether it is then the result of malignant transformation of a benign ulcer is debatable. Most authorities believe that chronic peptic ulcer rarely becomes malignant, and that malignant ulcers, however long they have been present, have been malignant from the start. Whatever the truth of the matter the problem in the individual case is to decide whether a given ulcer is benign or malignant.

Clinical Features. Unfortunately the majority of patients have advanced gastric carcinoma before they seek advice. In some there have been no symptoms; in others symptoms have been present for six months or even a year. Dyspepsia, which is at first vague, becomes troublesome with increasing anorexia and nausea, discomfort or pain, vomiting and weight loss. There may be cachexia and pallor, a mass may be palpable or peristalsis visible. The abdomen may be distended by ascites from peritoneal metastases. The prognosis in such patients is very poor, but if the cancer is detected early the outlook is better.

There being no specific symptoms, loss of appetite, slight nausea and discomfort after meals occurring for the first time in middle-age should always arouse suspicion. If the diagnosis is to be made early, then such patients require careful investigation. Early curable cancer may be missed at radiological examination or appearances may be misinterpreted; thus the only method of establishing a positive diagnosis is by gastroscopy and biopsies of suspicious areas. Carcinoma of the stomach should always be considered as a cause of unexplained iron deficiency anaemia, or as an uncommon cause of haematemesis or melaena. Tumours at the cardia may cause dysphagia, and tumours at the gastric outlet may cause vomiting. In the infiltrating type of tumour, diarrhoea may occur because of rapid emptying from the stomach. Sometimes it is the presence of metastases in the liver, pelvis or supraclavicular region which first brings the patient to the physician.

Radiology. The radiographic appearances vary. The commonest appearance is a filling defect in the antrum or body of the stomach (Fig. 67). If obstruction to the gastric outlet is present, it may not be possible to determine whether the lesion is benign or malignant until the stomach is aspirated and washed out. It may be difficult, if not impossible, to distinguish a malignant from a benign gastric ulcer; when doubt exists, and it commonly does, gastroscopy and biopsy should be performed. An early cancer may cause little more than distortion of the mucosal pattern which may be misinterpreted or go unobserved. A double contrast barium meal (p. 437) may overcome this difficulty. In the rare diffuse infiltrating scirrhous carcinoma, the radiograph is that of a rigid tube through which the barium pours rapidly into the intestine (Fig. 68). If dysphagia is the presenting symptom, a lesion in the cardia will probably be found, but symptomless lesions in this area can be very easily missed.

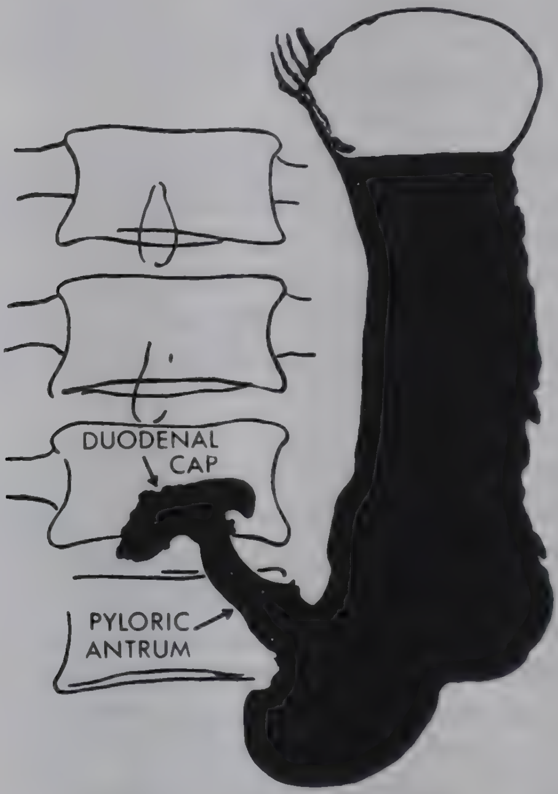


FIG. 67

Stomach following barium meal showing persistent narrowing of pyloric antrum—gastric carcinoma.

Other Investigations. Secretory studies may show diminished secretion of acid, but this is not of diagnostic value. Gastroscopy and biopsy should always be carried out when X-ray examination leaves any room for doubt. Exfoliative cytology will confirm the diagnosis of cancer of the stomach if the stomach washings contain obvious malignant cells. Examination of the blood may show hypochromic anaemia, with an elevated ESR. Finally, if these investigations are equivocal, laparotomy should be advised.

Treatment. The only curative treatment is gastrectomy, but it is usually only at laparotomy that the possibility of resection can be decided. Only about one-third of patients coming to operation are found to have tumours capable of removal; in the remainder it is possible to perform only a palliative procedure. This is worthwhile if pyloric obstruction is present, even if there are secondary deposits; such an operation relieves the distressing vomiting and gives the patient some comfort. A total gastrectomy may be required for tumours involving the upper part of the stomach. Careful pre-operative treatment is essential in order to get the patient as fit as possible; this may require the restoration of fluid and electrolyte balance and the correction of anaemia, while every effort should be made to improve the nutrition of the patient, if necessary by intravenous feeding.

Prognosis. The prognosis in carcinoma of the stomach is very poor and has shown little improvement in the last 40 years. The overall five-year survival rate is probably not more than 5 per cent. Of all patients with cancer of the stomach, only a small percentage find their way to hospital; of these about two-thirds are fit for operation, and radical removal is possible in about half of those who come to surgery. Among those who survive an apparently successful resection, the five-year survival rate is in the region of 20 per cent. Pending an entirely new approach to the problem, the only means currently available by which the prognosis can be improved is the detection of gastric cancer when it is at a curable stage; this requires a vigorous approach to the problem of dyspepsia in the middle-aged, including careful radiological and endoscopic examination and the critical follow-up of doubtful abnormalities.

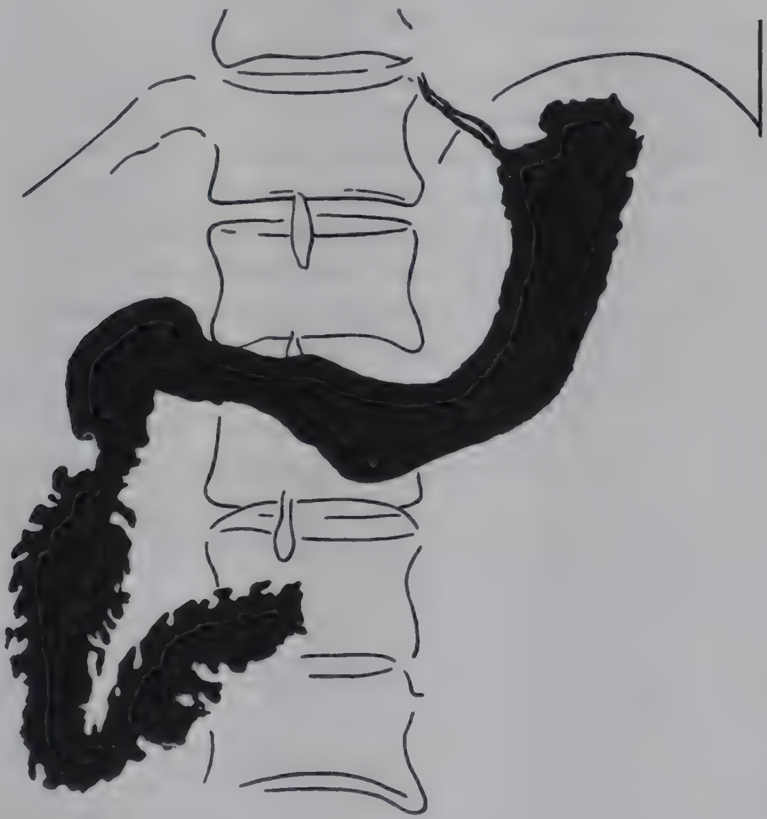


FIG. 68

Stomach following barium meal showing uniform narrowing with mucosal destruction and absence of peristalsis—diffuse infiltrating scirrhous carcinoma ('leather-bottle' stomach).

Malignant Ascites

Carcinoma of the stomach may be associated with the exudation of fluid into the peritoneal cavity. This follows the deposition of malignant cells on the peritoneal surface and is a sign of gross spread of the disease. The fluid is rich in protein and its sediment contains malignant cells which may be identifiable on microscopy. Other tumours which may be associated with a malignant ascites include carcinoma of the colon and carcinoma of the ovary.

Treatment is palliative. Relief of abdominal distension can be obtained by paracentesis, while instillation of antimitotic agents such as methotrexate may slow the rate of re-accumulation.

DISEASES OF THE PANCREAS

Anatomy and Physiology

The pancreas is a gland producing exocrine secretions which play important roles in digestion and also endocrine secretions concerned with the regulation of carbohydrate metabolism. The exocrine tissue, composed of tubulo-acinar glands of serous cells forms almost the entire mass of the gland. The exocrine secretion (the pancreatic juice) is discharged into the intestine through the pancreatic duct, which usually enters the duodenum together with the common bile duct at the sphincter of Oddi; in about 10 per cent of individuals, however, the main outflow of the pancreatic juice reaches the duodenum by a separate duct. The endocrine tissue is composed of specialised cells collected together in small islets (the islets of Langerhans) scattered throughout the gland, and accounts for only 1 per cent of the mass of the pancreas. The endocrine secretions are insulin, which is produced by the beta cells of the islets, and glucagon which is produced by the alpha cells; the functions of both substances are discussed in the section on diabetes mellitus (pp. 675).

Pancreatic juice is an alkaline secretion (pH 8·5-8·0) which is isotonic with plasma, the main cations being sodium and potassium while the main anion is bicarbonate. It contains three enzymes, namely amylase (diastase), lipase and trypsin. These enzymes are elaborated by the same serous cells of the pancreatic acini, and they are secreted in parallel concentrations; they all require an alkaline medium for optimal efficiency, so that theoretically digestion may be impaired if the bicarbonate content of the pancreatic juice is reduced.

Exocrine pancreatic secretion is stimulated partly through nervous and partly through hormonal mechanisms (p. 431), and a maximum flow is reached between two and three hours after a meal; in all, about one litre is secreted daily.

Investigation of the Pancreas

The pancreas is difficult to investigate. It is relatively inaccessible to direct methods of study and it cannot easily be examined by radiographic techniques.

Radiology. As yet there is no ideal radiological method of demonstrating pancreatic disease. A plain film of the abdomen may show calcification in the pancreas, and in acute pancreatitis this simple procedure may show a characteristic collection of gas in the hepatic flexure of the colon or jejunum—the 'sentinel loop'. A barium meal may show distortion of the mucosal folds of the duodenum or displacement of the stomach when the pancreas is enlarged by inflammation, cysts or tumours. An intravenous cholangiogram may show narrowing or distortion of the common bile duct due to neoplastic or inflammatory changes in the head of the pancreas.

Photoscanning (p. 439) following an intravenous injection of the isotope 75 selenium-methionine may reveal defects of uptake that suggest destruction of acinar tissue due to tumour or chronic inflammation.

Selective arteriography of the coeliac and superior mesenteric arteries can show distortion and compression of vessels from some tumours, or may outline the abnormal vascular pattern of others.

Pancreatograms can be obtained during operation by cannulation of the duct and injection of contrast material. In expert hands retrograde pancreatograms can be made using fibreoptic duodenoscopy (p. 440).

Tests of Exocrine Pancreatic Function. DIRECT TESTS. Pancreatic function may be tested directly by collection and analysis of pancreatic juice as described on page 442. In pancreatic insufficiency low volumes of secretion may be obtained with reduction in the concentration and output of bicarbonate and enzymes. In patients with carcinoma of the pancreas, the duodenal aspirate may contain blood and cytological examination may reveal exfoliated malignant cells. Fibreoptic duodenoscopy may allow the direct collection of pancreatic secretion for cytological examination.

INDIRECT TESTS. When pancreatic insufficiency is severe, the digestion of fat and protein is impaired and microscopy of the stool reveals abundant fat globules (steatorrhoea) and undigested meat fibres (creatorrhoea). This simple examination may be enough to detect pancreatic insufficiency in childhood but it is of less value in adults because fat globules and undigested meat fibres may be present in the stools of any patient with intestinal hurry. Steatorrhoea and creatorrhoea may be confirmed by chemical analysis of the faeces (p. 489).

Demonstration of a very high level of serum amylase is diagnostic of acute pancreatitis (p. 483). However, intermediate levels are less helpful since the enzyme may be elevated in other conditions such as intestinal obstruction and intestinal perforation. Sometimes acute pancreatitis may cause no elevation. Amylase is excreted by the healthy kidney, so that in acute pancreatitis the urinary levels may be greatly increased.

Tests of Endocrine Pancreatic Function. A diabetic glucose tolerance test in patients with steatorrhoea suggests a pancreatic cause for the malabsorption of fat. When carcinoma of the pancreas is suspected, an abnormal glucose tolerance test is a frequent and valuable finding in a condition difficult to diagnose.

Acute Pancreatitis

(ACUTE PANCREATIC NECROSIS)

This is a serious disorder which arises from autodigestion of the pancreas by its own enzymes and it may proceed to haemorrhagic necrosis of pancreatic tissue with the formation of a local or generalised peritonitis. The disease is most common between the fourth and seventh decades with an equal sex incidence.

The exact mechanism which initiates the destruction of the pancreatic tissue has not been established. The frequent association between biliary tract disease and acute pancreatitis has given rise to the widely accepted theory that an obstruction at the sphincter of Oddi due to a gall-stone, oedema or spasm allows a reflux of bile along the pancreatic duct. This causes an activation of the enzymes trypsin and lipase leading to autodigestion of the pancreatic blood vessels and parenchyma. Although in only a small proportion of cases can a stone be found at operation or post-mortem, a bile-stained pancreas is seen in many cases of acute pancreatitis and a common terminal channel for both the bile and pancreatic ducts is usually present in fatal cases. It seems unlikely that infection plays an initial role as cultures made in early cases are usually sterile. Once the process has started, however, oedema, haemorrhage and fat necrosis may continue, with destruction of much of the pancreas, with the liberation of a serosanguineous exudate into the peritoneal cavity, including the lesser sac, and with the chemical splitting of fat deposits in the omentum and mesentery. In Britain about 60 per cent of cases appear to be associated with underlying biliary disease and about 20 per cent with a history of alcoholic excess. The exact mechanism by which alcohol causes pancreatitis is unknown. In some countries, particularly the USA and South Africa, alcohol is a much more common cause of pancreatitis than in Britain. Acute pancreatitis may result from obstruction of the pancreatic duct due to carcinoma. Occasionally it occurs after abdominal trauma or surgery, and rarely as a complication of mumps, hyperparathyroidism, pregnancy or hypothermia.

Clinical Features. There is usually a history of preceding attacks of dyspepsia associated with pain in the back, and often of episodes of gall-stone colic. There may be a known history of alcoholism or recent contact with a case of mumps. The onset is sudden with agonising pain in the epigastrium or right hypochondrium. It often occurs within 12 to 24 hours following the taking of alcohol or a large meal. The pain is usually persistent and radiates most frequently through to the back, to either shoulder, or to one of the iliac fossae before spreading to involve the whole abdomen. Nausea and vomiting are frequent. The patient looks ill and in severe cases profound shock soon supervenes with cyanosis, clammy skin, rapid thready pulse and a subnormal temperature. In milder cases moderate fever occurs, and slight jaundice may develop, especially in cases with gall-stones.

Despite the severity of the pain, there may be little or no guarding of the abdominal muscles at first. Later the upper abdomen becomes tender and rigid as peritoneal irritation increases and the initial shock passes off.

Diagnosis. A most important point in the diagnosis of acute pancreatitis is for the practitioner to remember it as one of the causes of severe abdominal pain. About one-third of cases are proven for the first time at laparotomy, having been diagnosed as perforated peptic ulcer, acute intestinal obstruction or acute appendicitis. The condition may also simulate acute cholecystitis (with which it may co-exist), and myocardial infarction. In the early stage of an acute case the determination of the serum amylase is of great diagnostic importance. Within the first few hours levels in excess of 1,000 Wohlgemuth units per ml of serum may be found (normal 3 to 10 units). Such amylase estimations are useful only in the early stages of the acute disease since the concentration may be normal in mild cases and subsiding cases. Moreover the issue may be confused because moderate elevation of the serum amylase may occur in other conditions such as perforated peptic ulcer and intestinal obstruction. Serial estimations which show a rising level of serum amylase during the first 48 hours are of diagnostic value. Other laboratory investigations are of less help, but hyperglycaemia may occur and the blood calcium may fall in the later stages due to the formation of soaps from ionised calcium and fatty acids in the areas of fat necrosis. The serum bilirubin may be raised. There is usually a moderate polymorph leucocytosis. Radiological examination of the abdomen is essential. A plain film may show calcified gall-stones, calcification in the pancreas or in acute pancreatitis, a 'sentinel loop' (p. 480). Ileus and oedema of the duodenum may be demonstrated by Gastrografin studies.

Treatment. When the diagnosis of acute pancreatitis can be established with certainty, the present tendency is to avoid operation in favour of conservative treatment. However, laparotomy is imperative if diagnostic uncertainty exists.

Medical management consists of measures to combat shock, to relieve pain, to suppress pancreatic secretion and to prevent infection.

In the stage of shock, large volumes of saline, plasma or dextran are required and intravenous infusion may be necessary for several days to relieve dehydration and maintain electrolyte balance. Intravenous injections of calcium may be required if hypocalcaemia develops and blood sugar should be monitored regularly so that a developing diabetes can be treated promptly. For the relief of pain, repeated injections of methadone 10 mg or pethidine 100 mg should be given. If pain is very severe, hypodermic injections of morphine 10-20 mg may be required, but this drug, and pethidine to a lesser degree, may have the undesirable effect of causing spasm of the sphincter of Oddi. Pancreatic secretion may be inhibited in two ways. Continuous gastric suction reduces the amount of acid entering the duodenum, so that the stimulus for the production of secretin is greatly decreased; moreover continuous suction is of value in reducing vomiting and abdominal distension. Pancreatic secretion may also be diminished by anticholinergics which paralyse the nervous stimulation of the pancreas through the vagus nerve; gastric acid secretion will also be reduced because of vagal inhibition. Propantheline bromide is a synthetic drug which paralyses vagal function and may relax the sphincter of Oddi; it should be given in doses of 15-30 mg at six-hourly intervals. Alternatively atropine can be given in an initial dose of 1 mg, and thereafter 0·5 mg can be repeated at four-hourly intervals. Antibiotics may be administered with the object of preventing secondary bacterial infection of the damaged tissues. Corticosteroids have no specific place in the treatment of acute pancreatitis. The severe manifestations of acute pancreatitis are due in part to the release of vasoactive amines including kallikrein (p. 31) into the circulation with resulting hypotension and shock. Trasylol, a kallikrein inhibitor obtained from parotid gland tissue, has yet to be proved to be of therapeutic value.

Complications. Haemorrhage into the gastrointestinal tract because of digestion of the duodenal wall, or obstruction of the duodenum by the swollen pancreatic head may necessitate emergency surgery. Surgery at a later stage may be necessary for residual abscess, pseudocyst, or disease of the biliary tract.

Prognosis. Where recovery occurs from an attack of acute pancreatitis it is usually complete, and only a minority of such patients experience recurrent episodes or insidiously develop chronic pancreatitis. But the chronic alcoholic who continues to drink and the person with untreated biliary disease will suffer recurrent attacks.

Chronic Pancreatitis

This condition is due either to the laying down of excessive fibrous tissue in the pancreas as the result of recurrent inflammatory changes or to atrophy of acinar tissue following obstruction of a main duct. It may follow repeated attacks of acute or subacute pancreatitis or be associated with chronic inflammation of the biliary tract. It may occur following the penetration of a chronic duodenal ulcer into the pancreas. In many cases some cause of obstruction of the main pancreatic duct is found, including traumatic stricture, ampullary papilloma and stone. In these conditions when fibrosis is present, it is most marked between the lobules of epithelial cells, and whereas the acinar tissue is destroyed, the islet cells are spared for a long time. Pancreatic fibrosis of an intralobular type may occur in haemochromatosis with replacement of the parenchyma and early atrophy of the islet tissue.

A congenital form, known as mucoviscidosis or cystic fibrosis of the pancreas is associated with cystic dilatation of the acini and with congenital cystic disease of the lungs (p. 351); some of these patients survive to adult age. In certain parts of the tropics calcifying pancreatitis is common and may be related to protein deficiency in a highly alkaline vegetarian diet. It occurs in children and young adults and in many instances is not associated with the taking of alcohol.

Clinical Features. These depend on the nature of the associated primary disease, the amount of destruction of the acinar and islet tissue and the degree of obstruction of the common bile duct caused by the fibrotic and sometimes enlarged head of the pancreas. Chronic pancreatitis most commonly occurs in males in the fifth and sixth decades and many of these are alcoholics. Diffuse calcification of the sclerosed pancreas is usual in this group.

Pancreatic pain may be so characteristic that the diagnosis may be suggested on the history alone. It may be located in the epigastrium or in the right or left subcostal areas. The characteristic feature, however, is radiation of pain to the back relieved by crouching forward or by lying prone; sometimes the patient kneels crouching on the bed or leans forward over a chair to obtain relief. This type of pain occurs only in a proportion of patients, but if such a description is elicited, a pancreatic cause should always be suspected.

In some cases there may be no obvious clinical features and the condition is discovered only at autopsy or operation. Cases with haemochromatosis may show skin pigmentation (p. 566). In others marked loss of weight occurs because of faulty digestion and malabsorption; there is chronic diarrhoea with an excess of fat and undigested muscle fibres in the stools. Alternatively the condition may first manifest itself by the development of painless, slowly progressive obstructive jaundice with enlargement of the liver. There may be a previous history of symptoms of chronic cholecystitis and gall-stones. Ultimately the full picture of diabetes and malabsorption may supervene as both the acinar and islet tissues atrophy or are destroyed.

Diagnosis. A history of previous gall-bladder disease, especially cholelithiasis, or of excessive intake of alcohol, and succeeded by recurrent episodes of upper abdominal pain will usually be elicited. Characteristically the episodes of pain occur on the *day after* an occasion of dietary or alcoholic excess. In a proportion of cases of chronic pancreatitis the pancreas is seen to be calcified on straight X-ray of the abdomen. The calcification follows the distribution of the ducts which contain calculi or calcium-containing sludge. Pancreatic insufficiency may be suggested if steatorrhoea and an excessive output of faecal nitrogen are present on chemical analysis of the faeces collected over a period of five days. The diagnosis of pancreatic insufficiency is virtually certain if steatorrhoea is associated with a diabetic type of glucose tolerance curve, especially if xylose absorption is normal (p. 489). Serum amylase estimations are of little value in the diagnosis of chronic pancreatitis. Pancreatic function tests often demonstrate a low volume of secretion and reduced concentration of amylase and bicarbonate. The uptake in an isotope scan is poor and patchy or absent in advanced disease. Tests to demonstrate an increased salt content of sweat will be required if cystic fibrosis is suspected.

When jaundice is present the condition must be distinguished from: (1) stone in the common bile duct, in which there is usually intermittent pain, fever and fluctuating jaundice, (2) carcinoma of the head of the pancreas or of the bile duct, in which the features are so similar that even at laparotomy the diagnosis may be in doubt, and (3) chronic hepatitis with jaundice, in which there is some bile and an excess of fat in the stools.

Treatment. It is imperative that the patient stops drinking alcohol and remains abstinent permanently. The diet should be mixed with a moderately low fat content. If steatorrhoea is present the fat intake should be restricted to about 45 g daily.

Substitution therapy with adequate amounts of active pancreatic extracts is essential once steatorrhoea is present. The preparations should be taken both between and with meals and may be given as enteric coated capsules or tablets.

Insulin is required when, as is often the case, diabetes mellitus supervenes, and is necessary to allow the patient to continue to have sufficient carbohydrate to compensate for the decreased calorie intake associated with fat restriction.

Surgery should be contemplated for the relief of intractable pain. Drainage of the pancreatic duct into the small bowel, removal of part or most of the pancreas, or sphincterectomy are the most usual procedures. The ultimate result is so dependent on the patient's ability to give up alcohol that operation is not worth while in the patient who cannot do so. The indication for surgery is stronger when cysts and the possibility of cancer of the pancreas are present. The best results are obtained in those patients who are shown to have stones in the bile ducts or stenosis of the ampulla of Vater. Correction of these abnormalities will result in recovery of pancreatic function and the relief of symptoms.

Pancreatic Cysts

These are very rare and are broadly of three kinds: true acinous retention cysts of the ducts, proliferative cysts which are tumours, and the so-called pseudo-pancreatic cysts which result from the liberation of blood and pancreatic secretions into the lesser peritoneal sac. The last may occur after acute pancreatitis or follow rupture of the pancreas in injuries of the upper abdomen by impact or crushing.

Some cysts of the pancreas give rise to very few clinical features while others may cause mechanical effects, and pseudo-cysts may result in persistent pain. Such cysts present usually as a tense rounded swelling in the epigastrium, and diagnosis is facilitated by a barium meal, isotope scanning or selective arteriography. Operative treatment may be required and involves internal drainage into the alimentary tract, usually by anastomosis to the stomach or small intestine.

Tumours of the Pancreas

The two main tumours of the pancreas are carcinoma arising from the acinar epithelium and adenoma derived from the islets of Langerhans. Carcinoma arising from the ampulla of the bile duct is another important tumour occurring in this region.

Carcinoma of the Pancreas

This is an adenocarcinoma of scirrhous nature and in two-thirds of cases it is involvement of the head of the gland which causes symptoms and signs. It tends to spread early to neighbouring structures and to the liver. The condition is more common in males than in females, and occurs most frequently between the ages of 55 and 70 years.

Clinical Features. Epigastric pain, which is one of the earliest and most significant symptoms, may occasionally be absent throughout the course of the disease. The pain is variable in type but is characteristically dull and boring and radiates through to the back. It is often intensified by food and by lying supine, especially at night. It may be relieved by crouching forward. Vague dyspeptic symptoms are common and include anorexia, nausea, discomfort and sometimes vomiting. These symptoms may be the only manifestations until metastases occur.

Other clinical features depend largely on the site of the growth. In the majority of cases with involvement of the head of the pancreas jaundice is the presenting feature and may be painless and progressive. A large firm liver eventually develops. In such cases a dilated gall-bladder can frequently be palpated. Jaundice may not appear at all in cases where the lesion affects mainly the body and tail of the pancreas. The symptoms of diabetes mellitus may occasionally be the presenting feature in this disease. Carcinoma of the pancreas is a rapidly progressive emaciating disease especially in cases in which the head is involved, when death usually occurs within six months of the onset of obstructive jaundice.

Diagnosis. The condition has to be distinguished from: (1) chronic pancreatitis, (2) chronic hepatitis, (3) stone in the common bile duct, and (4) other causes of obstruction to the biliary passages, especially ampullary carcinoma. Radiological examination by barium meal may show distortion of the duodenal wall in carcinoma arising from the head of the pancreas and a forward displacement of the stomach in lesions of the body, but by then the tumour is almost certainly inoperable. Intravenous cholangiography in the absence of jaundice may reveal distortion of the common bile duct. In ampullary carcinoma fluctuating jaundice is common, and blood may be aspirated from the duodenum and be detected on testing the stool. Pancreatic function tests should be carried out and where facilities for exfoliative cytology are available the duodenal aspirate should be examined for malignant cells. Most of these investigations are superfluous in the patient with jaundice who has a palpable distended gall-bladder. In all cases where the symptoms are suggestive or where the cause of obstructive jaundice cannot be firmly established, exploratory laparotomy should be advised. Unless this is done, those cases of stone in the common bile duct in which pain is not a prominent feature may be erroneously diagnosed as carcinoma.

Endoscopy and scanning are discussed on pages 440 and 439.

Treatment. This is by surgical means. In carcinoma of the pancreas radical surgery is rarely possible, but a bypass may be fashioned to relieve the obstructive jaundice. Such patients, however, rarely live more than one year. In early cases of ampullary carcinoma a cure may be achieved by excision of the duodenum and head of the pancreas.

Islet-cell Tumours

Benign adenomas may arise rarely from the beta cells of the islets. They are usually very small and in 10 per cent of cases are multiple. They produce hyperinsulinism with attacks of spontaneous hypoglycaemia (p. 697). Even more rare are tumours, usually malignant, from non-specific islet cells which elaborate polypeptides, e.g. gastrin or allied substances, the secretion of which into the blood causes a variety of syndromes. The most common is the Zollinger Ellison syndrome (p. 470) in which gastric hypersecretion and persistent peptic ulceration are present. The treatment of these conditions is by the surgical removal of the adenomas where possible, or by total gastrectomy in the gastric hypersecretion syndrome.

DISEASES OF THE SMALL INTESTINE

Malabsorption

A number of disorders are encountered in clinical practice in which the primary effect is malabsorption of one or more of the necessary foodstuffs, mineral salts or vitamins. These disorders may be associated with some or all of the following features: diarrhoea, loss of weight, anaemia, mineral and vitamin deficiency, abdominal pain and distension. However, some patients complain only of vague ill-health, and the diagnosis may not be made for many years. Malabsorption is not synonymous with 'steatorrhoea', which means an excessive amount of fat in the stool, and not all patients with malabsorption have steatorrhoea.

The sequence followed in this section is first to review the basic processes of absorption and the means of testing them in clinical practice. Then the ways in which the processes of absorption can be deranged by disease or by surgery are discussed. Finally, the clinical presentation and treatment of specific disorders are described.

Absorption and Tests of Absorption

The absorption of substances necessary for metabolism is a complicated process often involving many sequential steps. Here is given a brief outline of the absorption of nutrients, vitamins and minerals together with the clinical tests which are used to measure their absorption. It should be appreciated that the clinical test provides only a crude assessment of absorption.

Fat Absorption. This takes place predominantly in the duodenum and upper jejunum. Dietary fat occurs largely in the form of insoluble long-chain triglycerides. These are emulsified mechanically in the stomach and by detergents (mainly bile) in the small intestine. Then pancreatic lipase hydrolyses the triglyceride to monoglyceride and fatty acids. Pancreatic bicarbonate is required to maintain the optimum pH for this hydrolysis and for the next step in fat absorption, the solubilisation of the monoglycerides and fatty acids by bile acids. This consists of their incorporation into aggregates called micelles which orientate the fatty acid and monoglyceride in such a way that they can be presented to the intestinal mucosal cell for absorption. Once in the absorptive cell, the monoglycerides and fatty acids are reformed (re-esterified) into triglycerides which then coalesce into chylomicrons. The chylomicron passes out of the cell to be transported by the lymphatic system into the blood.

The bile acids necessary for fat absorption are synthesised in the liver from cholesterol. They are then conjugated to either glycine or taurine and secreted into the bile, concentrated in the gall-bladder and released into the duodenum when the gall-bladder contracts. When they have performed their main function in forming micelles, they are absorbed from the terminal ileum. They are returned to the liver to be secreted once again into the bile—this is termed the enterohepatic circulation of bile salts.

TEST OF FAT ABSORPTION. Fat malabsorption is detected by measuring fat excretion in the stool over a five-day period, whilst the patient is receiving a normal diet (which contains less than 100 g fat per day). The upper limit of normal for faecal fat excretion is 7 g per day and any value above this constitutes steatorrhoea.

The fat-soluble vitamins A, D and K are absorbed in the same way as dietary fat and measurement of their absorption can be used as an indirect measurement of fat absorption. For example, the serum vitamin A level can be measured after two or three days of oral vitamin A.

Carbohydrate Absorption. Carbohydrate in the diet is in the form of starch (60 per cent), lactose (10 per cent) and sucrose (30 per cent). These are digested to glucose, galactose and fructose. Glucose and galactose are absorbed into the cell by active transport mechanisms, the process requiring sodium ions and energy. The fructose molecule is too large to move across the cell membrane by simple diffusion and it is thought that it must require a carrier. The process is called facilitated diffusion.

TESTS OF CARBOHYDRATE ABSORPTION. The oral glucose tolerance test (p. 684) is sometimes used and the absence of a rise in blood sugar can indicate malabsorption, but there are so many variables that the test is difficult to interpret in the context of absorption.

In the xylose absorption test, 25 g of d-xylose are given orally after an overnight fast. Only a small proportion is metabolised within the body and 5-8 g should be excreted in the urine over the next five hours.

In the lactose tolerance test, 50 g of lactose are given orally and blood glucose levels are measured as in the glucose tolerance test. If the enzyme lactase is deficient in the intestinal mucosa, there may be no rise in blood glucose and the patient may complain of colic and diarrhoea because the unabsorbed lactose acts as an osmotic agent in the gut before being broken down by colonic bacteria into lactic acid and carbon dioxide (p. 494—lactose intolerance).

Protein Absorption. Initial hydrolysis of dietary protein molecules is performed by gastric pepsin and pancreatic enzymes. Further hydrolysis of peptides takes place at the brush border and a mixture of peptides and amino acids is absorbed into the cell. A large amount of protein, other than dietary, enters the lumen of the gastrointestinal tract each day, derived from various secretions, desquamated cells and the exudation of plasma proteins. These proteins are absorbed by the same mechanisms as dietary protein.

TESTS OF PROTEIN ABSORPTION. Measurement of the amount of nitrogen in the stool provides a very crude estimate of the above processes. Stools are collected for three to five days and no more than 2·5 g of nitrogen per day should be excreted.

An excessive loss of nitrogen in the stool can result from the loss of albumin and other plasma proteins into the lumen of the tract. This is termed 'protein losing enteropathy' and it can be detected by labelling serum proteins with radioactive iodine, chromium or iron and measuring radioactivity in the stool.

A low serum albumin level in the absence of hepatic or renal disease may indicate protein malabsorption.

Folate absorption. Folate is absorbed throughout the small intestine by an active transport process. In tests of folate absorption a large quantity of folic acid is given to saturate body stores, then a test dose is given orally. Folate is then measured in the blood or urine by microbiological assay. Some tests make use of radioactive folic acid.

Vitamin B_{12} Absorption. Dietary vitamin B_{12} binds to intrinsic factor in the stomach and proceeds along the intestine in this bound form to be absorbed from the terminal ileum.

In clinical practice, absorption is measured by giving the fasting patient a small oral dose of vitamin B_{12} labelled with radioactive cobalt (the *Schilling test*). Two hours later a large dose of non-radioactive B_{12} is given by injection and the urine is collected for 24 hours. The injected vitamin B_{12} saturates the plasma so that the absorbed radioactive vitamin B_{12} is excreted in the urine. In a normal subject more than 16 per cent of the oral dose should be excreted in the urine. A normal result is also obtained if intrinsic factor is given together with radioactive vitamin B_{12} to a patient with Addisonian pernicious anaemia but not in patients in whom there is malabsorption of vitamin B_{12} due to disease of the terminal ileum.

Absorption of Other Substances. Calcium is absorbed in the upper small intestine by an active mechanism which requires vitamin D. Iron is also absorbed by the proximal small intestine in an ionic form and as haem. Suitable diagnostic tests of the absorption of these substances are not available but the degree of absorption can be inferred from the serum levels. For example, a low serum iron level may indicate malabsorption if there is no evidence of blood loss or inadequate intake. Similarly a low serum calcium level may indicate vitamin D deficiency due to malabsorption.

Causes of Malabsorption

These may be classified as follows:

1. **Disorders of Intraluminal Digestion.** In these disorders the intestinal mucosa is normal but there is an insufficiency of a digestive enzyme or detergent within the lumen. The main feature is steatorrhoea with deficiency of fat soluble vitamins. Since the intestinal mucosal cells are normal, the absorption of other substances, less dependent on intraluminal digestion, is normal; thus the absorption of carbohydrate, protein, vitamin B_{12} folic acid and iron is unimpaired.

(*a*) PANCREATIC INSUFFICIENCY. A deficiency of pancreatic lipase causes malabsorption of fat, for example, in chronic pancreatitis, carcinoma of the pancreas or mucoviscidosis (p. 351).

(*b*) DEFICIENCY OF BILE ACIDS. This may occur in two circumstances:

(i) *Interruption of the Enterohepatic Circulation of Bile Acids.* When there is disease or resection of the terminal ileum, as in Crohn's disease, bile acids cannot be reabsorbed. Instead they are passed into the colon and are lost in the faeces. Whilst in the colon they interfere with water and electrolyte absorption and this results in diarrhoea. The loss of bile acids cannot be compensated for by the liver synthesising more bile acids. There is therefore an inadequate concentration of bile acids in the upper jejunum and micelles cannot be formed.

(ii) *Colonisation of the Small Bowel by Bacteria.* The upper part of the small intestine is practically sterile under normal conditions. If a large number of bacteria are present as in the 'blind loop syndrome' (p. 494) then some of these bacteria may deconjugate bile acids, i.e. the glycine or taurine is split from the molecule. The deconjugated bile acids are inefficient in micelle formation and so steatorrhoea results.

Colonisation can affect other aspects of the intraluminal phase. For example, bacteria can utilise amino acids which are about to be absorbed and they may also take up vitamin B_{12} so that it is unavailable for absorption in the terminal ileum.

(*c*) DISORDERS OF GASTRIC RESECTION AND HYPERSECRETION. After gastric surgery it is possible for the correct enzymes, detergents and electrolytes to be delivered into the intestinal lumen and yet malabsorption may occur. This is because the digestive process is no longer coordinated. For example, after gastro-enterostomy or a Polya partial gastrectomy, it is possible for bile and pancreatic juice to be delivered after food from the stomach has already passed down the efferent loop. Gastric emptying is no longer coordinated with the correct stage of digestion.

Problems can also arise in the Zollinger Ellison syndrome (p. 470). A large volume of acid may pass into the upper small intestine and if this is inadequately neutralised it will denature pancreatic enzymes and in addition the pH will be too low for micelle formation.

2. **Disorders of Mucosal Cell Transport.** In these disorders, the intraluminal digestive phase is normal, but the absorptive cells are abnormal.

(*a*) GENERALISED DISORDERS. Here an abnormality of the mucosa or absorptive cell can be seen histologically as, for example, in coeliac disease, tropical sprue and extensive Crohn's disease of the small intestine. In these conditions, because the mucosa is damaged, it is usual to find widespread disorders of absorption. Thus, in addition to steatorrhoea, there may be malabsorption of xylose, folic acid, vitamin B_{12} and low levels of serum iron, calcium and albumin are common.

(*b*) SPECIFIC DISORDERS. Here the mucosa looks normal but a specific substance is malabsorbed because of the absence of a particular enzyme. Thus there may be malabsorption of lactose because of an insufficiency of lactase in the mucosa. Another example is the malabsorption of vitamin B_{12} because of a lack of intrinsic factor in pernicious anaemia.

3. **Disorders of Transport from the Mucosal Cell.** These are rare disorders which result from the blockage of the lymphatic system which is responsible for the transfer of chylomicrons from the absorptive cell to the systemic circulation. This may occur in abdominal lymphoma or in the rare condition of primary lymphangiectasia in which the mesenteric lymphatic system is abnormal.

Clinical Features of Malabsorption. The patient can present in various ways. In severe forms there may be general malnutrition, with loss of weight and energy and a slow deterioration in health or, in a child, a failure to grow and thrive. Abdominal distension is often a striking feature. Steatorrhoea may be the presenting symptom: The patient complains of diarrhoea, with the passage of loose, pale, bulky and offensive stools which float on water, so that to cleanse the toilet-pan may require several flushes from the cistern. This difficulty is almost pathognomonic of steatorrhoea. The patient may have an anaemia which is the direct consequence of a deficiency of iron, cyanocobalamin or of folate. Apart from changes in the blood picture, haemorrhagic phenomena due to a deficiency of vitamin K may be an occasional presenting feature. Tetany may occur as a result of hypocalcaemia. The features of rickets or osteomalacia and various other disorders due to deficiency of vitamins may be noted, such as sore tongue, angular stomatitis and dry and atrophic skin. Oedema may occur as a consequence of hypoalbuminaemia. In other patients, malabsorption may be suspected because of gastric surgery or intestinal resection. In patients with mild malabsorption, there may be no disturbance of bowel function and the condition may be diagnosed only after investigation for non-specific abdominal complaints or anaemia.

Diagnosis. The diagnosis may be suspected on clinical grounds or as a result of a barium follow through examination in a patient with abdominal symptoms. The small intestine shows dilated loops with flocculation and segmentation of barium.

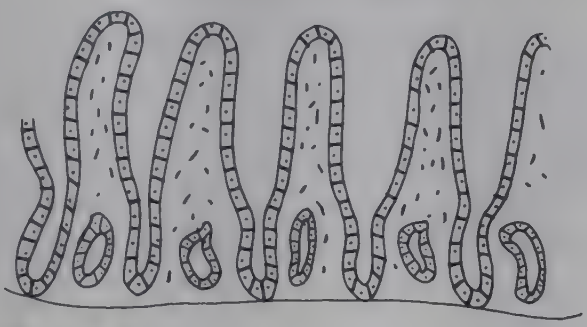
Malabsorption is confirmed by the tests of absorption which may also provide a clue as to the basic cause of the disorder. For example, malabsorption of several substances is likely when there is a generalised disorder of the absorptive cells.

Biopsy of the small intestine (p. 440) is the most important investigation. The biopsy may be normal, which excludes coeliac disease, or it may show subtotal villous atrophy, which is diagnostic of coeliac disease. Partial villous atrophy can occur in a variety of disorders, such as tropical sprue, Crohn's disease and in mild cases of coeliac disease (Fig. 69). Obviously, if the intestinal biopsy is normal, other investigations may be necessary to provide the diagnosis—for example, pancreatic function tests (p. 442) or the culture of intestinal aspirates for bacteria.

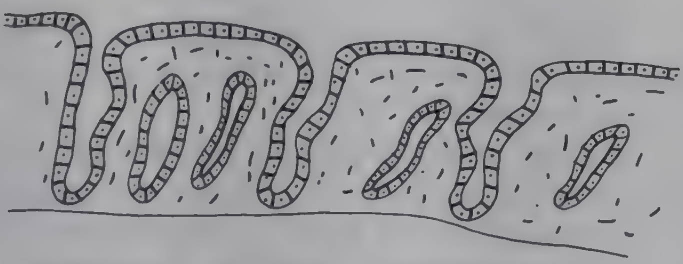
The Principal Disorders of Malabsorption and their Treatment

Coeliac Disease in the Child and Adult

Coeliac disease is characterised by an abnormal mucosa in the small intestine which results in the malabsorption of several nutrients. In most cases the abnormality is due to a sensitivity to gluten. The term 'coeliac disease' was applied originally to the form of malabsorption that develops in children soon after weaning and eventually it came to be applied to malabsorption in adults. Gluten is a protein contained in wheat and rye flour, and in some way as yet unexplained it damages the mucosa of the small intestine in susceptible individuals. The toxic agent is gliadin, a polypeptide component of gluten, but it is not known what determines the susceptibility of an individual patient to the effects of gliadin, nor indeed how the toxic effects are induced.



NORMAL



SUBTOTAL VILLOUS ATROPHY

FIG. 69

Histological appearances of the mucosa of the small intestine.

Gluten-induced enteropathy usually begins within the first three years of life. The child ceases to thrive and becomes fractious and irritable, the stools become voluminous and pale and as the disorder progresses growth is retarded, iron deficiency anaemia develops, and the abdomen becomes distended. On the other hand, the disorder may manifest itself for the first time in adult life. In adults, the presenting symptoms range from those of a mild anaemia and listlessness of long duration, to a florid malabsorptive state developing rapidly over a period of weeks or months. The commonest features are diarrhoea, weight loss and anaemia, the anaemia being usually due to combined deficiency of folic acid and iron. Gluten-induced enteropathy appears to predispose to the development of lymphomas and other forms of malignancy in the alimentary tract; colicky abdominal pain and unexpected weight loss in a previously well-controlled patient with malabsorption should arouse suspicion of these complications.

Treatment. A gluten-free diet (Diet No. 15, p. 1005) must be given for many years or for life. This can result in histological improvement in the intestinal mucosa and improvement in absorption. If a small amount of gluten remains in the diet, the patient may fail to respond, and so the patient is given strict diet sheets and recipes for the use of gluten-free flour. A booklet produced by the Coeliac Society is of great value in this regard and should be strongly recommended (p. 1005). In patients who fail to respond it may be necessary to use corticosteroids. Mineral and vitamin supplements are also given when indicated.

Lactose Intolerance

This disorder is being seen more often in Britain because immigrant Asian and African races have insufficient lactase in the mucosa of the small intestine to digest the large amounts of lactose consumed in this country.

The patient complains of abdominal discomfort, colic and diarrhoea after the ingestion of milk or milk products. The symptoms can be reproduced by the lactose tolerance test (p. 489) and the condition responds to the reduction of lactose in the diet.

Blind Loop Syndrome

In this condition, there is an excessive proliferation of bacteria in areas of the upper gastrointestinal tract which are normally sterile. The effects of this proliferation have been discussed (p. 491).

The presentation is with anaemia due to vitamin B_{12} deficiency or with diarrhoea and nutritional deficiencies. The diagnosis depends on the radiological demonstration of a causative lesion in the intestine (Fig. 70) and on the correction of the steatorrhoea and vitamin B_{12} malabsorption by broad spectrum antibiotics. The causative lesion usually consists of an area of the intestine where bacteria can proliferate without being subjected to movement down the intestine, for example, jejunal diverticula or the afferent loop after gastric surgery. Other causes are disordered peristalsis in the small intestine and fistulae from the upper small intestine to the colon which allow colonic bacteria to enter the small intestine.

Treatment. Treatment is with broad spectrum antibiotics and dietary and vitamin supplements. Occasionally it may be necessary to correct a structural abnormality by surgical means.

Malabsorption in Crohn's Disease

Malabsorption occurs for a variety of reasons in Crohn's disease (p. 496). The enterohepatic bile salt circulation may be interrupted by disease or resection of the ileum. Other areas of the small intestine may be involved, thus reducing the surface area for absorption. Strictures and fistulae may lead to the blind loop syndrome. The inflamed mucosa may allow plasma proteins to be lost so that there is a protein losing enteropathy. Thus a variety of nutritional abnormalities may result which require the administration of dietary and vitamin supplements.

Malabsorption after Gastric Surgery

Again a variety of causes may be responsible, for example, poor mixing of food and digestive secretions and blind loop syndrome. These problems are discussed on pages 491 and 494.

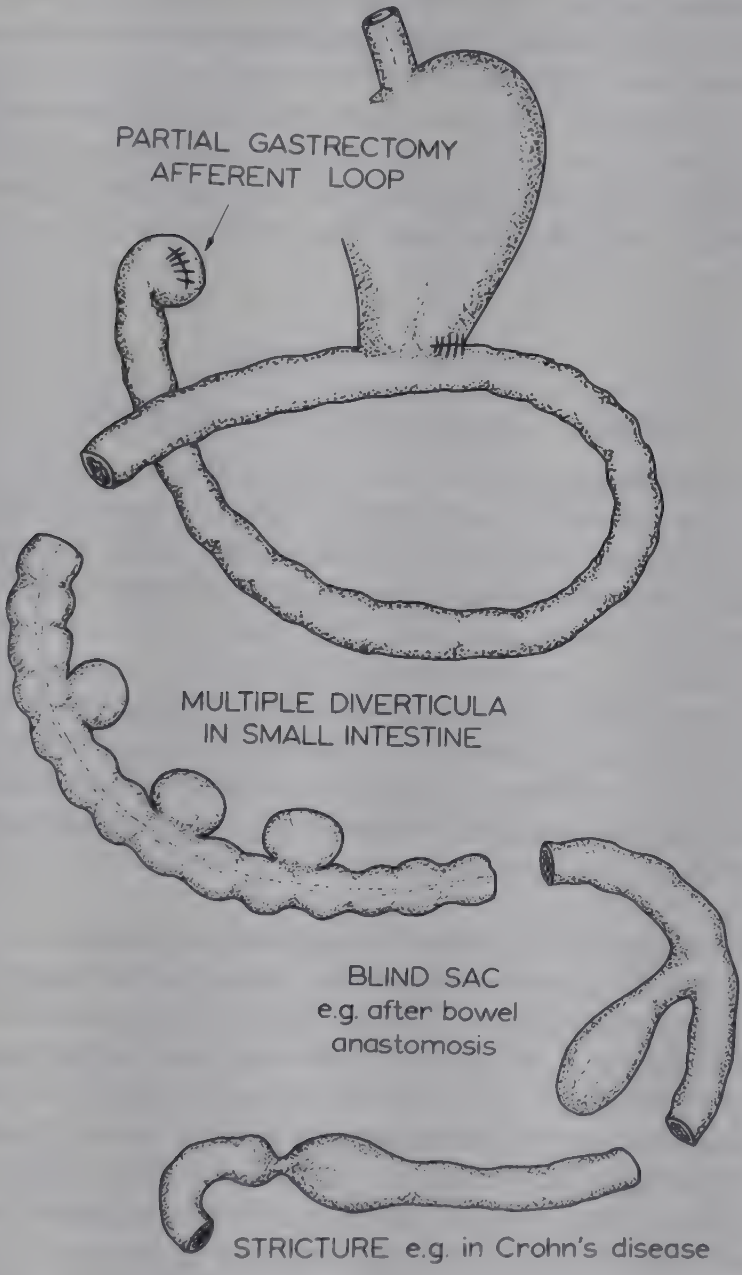


FIG. 70

Blind loop syndrome may arise because of stasis in the afferent loop in partial gastrectomy, in diverticula, in a blind sac or in the bowel proximal to a stricture.

TREATMENT OF MALABSORPTION

Some forms of treatment have been described, e.g. gluten-free diet. Pancreatic insufficiency is treated by pancreatic supplements (p. 485). Insufficiency of bile salts should not be treated with oral bile salts because these would pass into the colon, interfere with salt and water absorption (p. 491), and so worsen the diarrhoea. Thus treatment of diarrhoea is aimed at counteracting the effect of the endogenous bile salts on the colon by giving the binding agent cholestyramine in a dose of up to 12 g per day. In addition, a low fat diet should be given because cholestyramine will not correct the steatorrhoea.

In severe forms of malabsorptive disease, it may be necessary to correct dehydration and electrolyte deficiency by intravenous infusions.

Supplements are often necessary for those patients with anaemia, bone disease or coagulation defects. Folic acid and iron supplements are given orally and vitamin B_{12} by a monthly injection. Vitamin D and calcium supplements may be required. Calcium is normally given as gluconate or lactate by mouth, but when there is tetany 10 ml of 10 per cent calcium gluconate is given slowly intravenously. Glossitis and cheilosis are indications for the administration of vitamin B complex.

Crohn's Disease

(Regional Ileitis; Regional Enteritis)

This disease is characterised by localised areas of non-specific, granulomatous inflammation of the bowel. It was formerly termed regional ileitis, since it was considered to be a disease confined to the terminal ileum. However, the eponymous designation 'Crohn's disease' is perhaps preferable since it is now known that it can affect the alimentary tract from the mouth to the anus, the sites most commonly involved being, in order of frequency, terminal ileum, terminal ileum and right side of colon, colon alone, ileum and jejunum. The disease may occur at any age, but most commonly between the ages of 20 and 40; it affects both sexes equally. In its chronic form, it is a debilitating disease which often interferes profoundly with a patient's life requiring repeated admission to hospital for medical and surgical treatment.

Aetiology. The cause is unknown. No specific organism has been identified from the bowel content, the bowel wall or the regional lymph nodes. One of the histological characteristics of the disease is the presence of granulomas composed of collections of epithelioid cells and giant cells. These granulomas closely resemble those found both in tuberculosis and sarcoidosis, thus raising the possibility that the three diseases are related. However, Crohn's disease can be sharply distinguished from tuberculosis because of the absence of caseation in the affected areas. Although the histological differentiation from sarcoidosis is more difficult, it is now universally accepted that these two diseases are not related, since the clinical course is so different. Like sarcoidosis, however, patients with Crohn's disease show deficiencies in delayed-type hypersensitivity, presumably indicating impaired cellular immunity. A current hypothesis is that Crohn's disease is the consequence of an abnormal immune response in the gut wall to an unidentified antigen. A hereditary factor is suggested by the increased incidence of the disease amongst people of the Jewish race, as well as an increased familial incidence; Crohn's disease, ankylosing spondylitis and ulcerative colitis all occur more commonly than might be expected amongst the families of patients with Crohn's disease, suggesting that all three diseases share a common but incomplete genetic basis.

Pathology. Although the disease may affect any part of the alimentary canal, the terminal ileum is most often involved. Macroscopically, the bowel is engorged and oedematous so that the lumen is markedly narrowed, sometimes enough to produce obstruction; the mucosa is oedematous, showing a 'cobblestone' pattern with linear ulceration and fissuring. Characteristically, these changes are patchy; even when a relatively short segment of bowel is affected, it can be seen that the inflammatory process is interrupted by islands of normal mucosa occurring in the diseased area, the change from normal mucosa to the affected part being abrupt. The lesions may be discontinuous over a length of the bowel, a small lesion separated in this way from a major area of involvement being referred to as a 'skip' lesion. The affected lymph nodes are enlarged and the mesentery thickened. Microscopically, inflammatory change involves all coats of the bowel wall. All grades of inflammation may be seen and characteristically there is oedema and hyperplasia of the lymphoid follicles. Granulomas are seen in about 50 per cent of cases. Another feature is the presence of deep clefts or fissures opening on to the mucosal surface and sometimes passing through the entire thickness of the bowel wall. These clefts are responsible for the fistula formation which is such a characteristic feature of the disease; fistulae may develop between adjacent loops of bowel or between affected segments of bowel and the bladder, uterus or vagina, or may present as a faecal fistula through an abdominal incision as a complication of surgical treatment.

Clinical Features. The clinical features depend in part on the site and extent of the bowel affected. Crohn's disease may present acutely with features indistinguishable from acute appendicitis and so the diagnosis is made at laparotomy. At operation, the terminal ileum is red and oedematous and provided the abdomen is closed without resection the prognosis is relatively good.

In the chronic form of the disease, pain is the commonest symptom and may be due either to peritoneal involvement, obstruction or both. Since the terminal ileum and right side of the colon are most commonly affected, this type of pain occurs most frequently in the right lower quadrant and it may be associated with local tenderness or guarding. A mass is palpable by abdominal and frequently by rectal examination. This consists of inflamed loops of bowel bound together, possibly including an abscess, and may be of any size. Colicky pain suggests obstruction, and may be associated with nausea and vomiting and excessive borborygmi. Indeed, recurrent episodes of colic due to attacks of subacute obstruction are a prominent feature in the life history of a patient with Crohn's disease; however, severe acute obstruction is uncommon.

Diarrhoea is frequent, but is rarely so marked as in ulcerative colitis. The stools may be formed or loose, and rarely contain frank blood, mucus or pus unless the colon is involved. A diagnostic feature, when present, is the occurrence of anal lesions such as oedematous skin tags or perianal abscesses and fistulae. These lesions may occur when only the small bowel is involved, though they are more common when the colon is affected.

Weight loss is frequent and most patients have a low-grade fever and moderate anaemia. Clubbing of the fingers may be present. A number of systemic manifestations may occur, including arthritis, ankylosing spondylitis, iritis, aphthous stomatitis and erythema nodosum; the relationship between these systemic disorders and the bowel is not clear. Minor degrees of liver damage with abnormal liver function tests are relatively common, while renal complications include hydronephrosis due to involvement of the right ureter in an inflammatory mass.

Radiological Examination. Barium meal and follow-through examination may show alteration of the mucosal pattern, deep ulceration or the pathognomonic 'string sign' due to marked narrowing of a segment of affected bowel. The lesions tend to be discontinuous along the length of the bowel giving the characteristic appearances of 'skip' lesions. A barium enema should always be carried out since the disease may affect the small bowel and the colon simultaneously. In about 50 per cent of cases, the caecum will show radiological abnormalities. In some instances there will be segmental areas of deep ulceration or stricture formation elsewhere in the colon, and occasionally the entire colon is involved so that the radiological appearances may be indistinguishable from ulcerative colitis (p. 511).

Laboratory Investigations. Pus cells and red blood corpuscles may be found on microscopic examination of the faeces, but culture of the stool yields no specific organism. Moderate anaemia is usually present because of blood loss, while protein loss from the inflamed, ulcerated mucosa may cause hypoproteinaemia. Vitamin B_{12} absorption is likely to be impaired if there is extensive disease of the terminal ileum, and this can be confirmed by an abnormal Schilling test (p. 490). The diagnosis may be confirmed either by rectal biopsy or by surgical excision of perianal skin tags; a rectal biopsy will sometimes show the characteristic granulomatous lesions although the mucosa appears normal to the naked eye.

Differential Diagnosis. The symptoms, signs and radiological findings are usually sufficient to suggest a lesion in the lower part of the small bowel. The other common diseases in this part of the intestinal tract are appendicitis or an appendix abscess, carcinoma of the caecum and, rarely in Britain, tuberculosis of the ileo-caecal region, and caecal amoebiasis. In the acute phase, it may be impossible to distinguish between these possibilities, so that a laparotomy may be necessary. In patients with a chronic illness, the diagnosis may be established by further investigation—for instance, a barium enema examination or by biopsy of the rectum or perianal skin lesions. Although tuberculosis of the ileo-caecal region is becoming rare in Britain it may occur in the immigrant population and should always be borne in mind because of the possibility of cure. Ileo-caecal tuberculosis usually occurs in association with an obvious pulmonary lesion so that the diagnosis is suggested by the chest X-ray; however, it can sometimes occur in patients in whom the primary lung lesion is minimal and has been overlooked. A 'negative' tuberculin test (p. 360) is common in patients with Crohn's disease and excludes an active tuberculous process. Sometimes no conclusive proof of Crohn's disease is obtained, and the diagnosis can only be presumptive; such patients should be kept under observation until the natural history of the illness declares itself.

Treatment. Crohn's disease is a chronic condition with remissions and relapses over many years. There is no known cure at present and treatment is largely a matter of managing particular problems as they arise and improving the general condition of the patient.

GENERAL MEASURES. A low residue diet will reduce the frequency of intestinal colic, while diarrhoea may be reduced by the use of codeine, 30 mg four times daily. When the terminal ileum is extensively diseased or has been resected, cholestyramine will reduce the diarrhoea due to the cathartic effect of the unabsorbed bile salts on the colon; cyanacobalamin should be given to such patients for life as in pernicious anaemia (p. 730) since vitamin B_{12} will not be absorbed if the terminal ileum is involved.

Malabsorption with steatorrhoea may occur in patients with extensive involvement of the small intestine, contributing to weight loss and inanition. Treatment of such patients may require a low fat diet and a course of oral antibiotics if bacterial colonisation of the upper intestine is suspected as the cause of symptoms or malabsorption. Oral supplements of iron, folic acid, calcium and vitamins may also be necessary and electrolyte deficiencies, especially of potassium, may require oral or intravenous replacement. Hypoproteinaemia may require plasma or blood infusions in addition to a high protein diet.

DRUGS. Although there is no specific cure for Crohn's disease, there is no doubt that corticosteroids may induce remission in patients with active disease presenting with fever and weight loss. Prednisolone should be given in a dose of 40-60 mg daily in divided doses for 1 or 2 weeks depending on response, and the dose gradually reduced thereafter to 10-20 mg daily for four to six weeks and then withdrawn. Every effort should be made to stop the drug, but in the occasional case this may be difficult because of early relapse when the dose is reduced. In these circumstances, the effect of sulphasalazine (2-4 g daily is worth a trial, much as it is used in ulcerative colitis (p. 513). In contrast to colitis, oral antibiotics may be of some benefit, and a course of ampicillin, 1-2 g daily for four to six weeks can be tried, especially in patients with mild disease or in those not responding to prednisolone. Treatment with immunosuppressant drugs has been tried in patients unresponsive to other forms of therapy.

SURGICAL TREATMENT. Although attacks of subacute obstruction can usually be managed conservatively by intestinal decompression and intravenous feeding (p. 503), operation may be necessary if attacks occur frequently. Surgical intervention may also be required because of abscess or fistula formation. There is no unanimity as to the correct surgical treatment in any of these circumstances, the principal alternatives being resection of the diseased segment or a bypass procedure. With localised disease, resection yields better results than bypass, but with extensive disease massive resection may result in malabsorption. Recurrence of the disease is always a danger, and therefore as much bowel as possible should be preserved. Resection nevertheless is indicated for the management of intestinal, vesical and vaginal fistulae. When the colon is extensively involved a total proctocolectomy as in ulcerative colitis (p. 514) may be the surgical procedure of choice, though less extensive resection, for example a right hemicolectomy may suffice for localised disease.

The Acute Abdomen

The term 'acute abdomen' embraces a variety of abdominal conditions which have in common sudden onset, severe and progressive upset to the patient and a high risk of death. The responsible disease need not necessarily originate in the alimentary tract, because acute abdominal symptoms may stem from disease of other systems, as, for example, the urogenital tract or vascular system. In general the acute abdominal episode is due to peritonitis, intestinal obstruction, haemorrhage, renal or biliary colic.

Although accurate diagnosis may be ideal, in practice it is not always possible. It is more important to recognise the urgency of the situation and its potential danger. Time-consuming tests and biochemical studies are unjustifiable, for there is risk in delay, and laparotomy is indicated in the majority of cases —hence the aphorism, it is safer to look and see than wait and see. The purpose of pre-operative investigation is to define those few conditions that might safely, or with benefit, be treated conservatively, and to eliminate the few 'medical' conditions such as lobar pneumonia and myocardial infarction that can mimic the acute abdomen. Otherwise, pre-operative investigation serves to guide the surgeon in his approach and his measures of resuscitation. There is no entirely satisfactory classification; in the western hemisphere, the most common causes of the acute abdomen are: appendicitis, perforated duodenal ulcer, acute cholecystitis, intestinal obstruction, renal colic, ectopic gestation and mesenteric thrombosis or embolism.

In no other branch of medicine has the diagnostician so complete an opportunity to exercise his clinical judgement and in no other branch is his decision so vital.

Examination of the Acute Abdomen. The *history* is all important. Attention must be paid to the description of the onset of the pain, where it started, whether it radiated, and whether it has remained constant or is intermittent. Its severity may be difficult to judge in some, but in others it will be obvious from the degree of general disturbance. The pain of peritonitis, particularly when due to perforation of an ulcer, causes the patient to lie still, whereas in the biliary and renal colics he writhes in his search for relief.

Physical examination must be general and in addition to the abdomen must include particularly the lungs, heart and the hernial orifices.

Abdominal examination starts with *inspection* in a good light, the patient lying flat with the head supported on a pillow. Observation should be unhurried. The movement of the abdominal wall, any general or local restriction, should be noted along with any asymmetry caused by distension of bowel loops. In a thin subject the peristalsis in obstructed bowel may be seen, and the gurgling of the contracting bowel may be heard.

Palpation must be gentle, as causing pain only results in contraction of the abdominal muscles and prevents detection of intra-abdominal masses. Palpation of a distended caecum in large bowel obstruction, of an inflamed gall-bladder, of an intussusception, or of an appendix mass can virtually make the diagnosis. Demonstration of guarding and rigidity indicates peritoneal irritation, and when this is localised to a particular area it points to disease of underlying structures.

Light percussion may confirm gas distension of bowel loops, or show loss of liver dullness in perforation of a peptic ulcer.

Auscultation should always be practised. There is no mistaking the rush of bowel sounds in intestinal obstruction, particularly if associated with a wave of abdominal pain. Exact localisation of the source of noise may indicate the site of the obstruction, while the silence of generalised peritonitis is equally impressive in its sinister significance.

No clinical examination of the abdomen is complete without *digital examination of the rectum* to detect abnormalities in the peritoneal pouch. Careful *palpation of the groins* is also essential to exclude hernia. In the overall assessment of the patient, it is important to remember that signs of peritonitis and of strangulation can be masked by sedatives such as morphine, while the improvement produced by naso-gastric suction in bowel obstruction can be misleading.

Investigations. Urinary examination is essential; it may show blood in renal colic, pus in acute pyelonephritis, bile in obstructive jaundice, sugar in pancreatitis, sugar and ketones in diabetic ketoacidosis and porphobilinogen in intermittent acute porphyria. Other useful laboratory examinations include a white blood cell count and estimation of serum amylase.

Plain X-rays of the abdomen, taken erect and supine, are invaluable in demonstrating perforation of a hollow viscus, peritonitis and intestinal obstruction. Gas under the diaphragm, indicative of perforation, may be more clearly seen on the chest X-ray.

If myocardial infarction is suspected, an electrocardiogram must be obtained. Occasionally the stress of an abdominal catastrophe may provoke coronary thrombosis so that the two co-exist.

Management. It is customary to advise that in all cases of acute abdomen an early surgical opinion be sought, but better still is the adoption of a combined approach by physician and surgeon to all difficult abdominal problems.

Intestinal Obstruction

Intestinal obstruction may be complete or incomplete, acute or chronic, intermittent or continuous. In some of its less severe forms it has to be distinguished from constipation and from other causes of abdominal distension.

Classification. The most important point to decide is whether the obstruction is *simple* or associated with *strangulation*. The latter occurs when there is interference with the blood supply to the intestine, as when the bowel is trapped or twisted. Urgent relief is required if the dangers of gangrene, perforation and peritonitis are to be avoided.

Obstruction may be *mechanical*, when the lumen of the bowel is blocked, *or paralytic*, when the propulsive power of the bowel is lost. In general the former type will require surgical relief, while the latter may respond to conservative measures, but the distinction is not always clear cut. Sometimes the mechanically obstructed bowel becomes exhausted and non-contractile, or it perforates at the site of the obstruction or proximally, the resultant peritonitis being responsible for paralysis of the adjacent bowel loops.

Causes. A. MECHANICAL OBSTRUCTION. At all ages adhesions and hernias are common causes of obstruction. In the young, intussusception is a frequent cause, while in the elderly, volvulus, tumours of the large bowel and diverticular disease account for a large proportion of cases. Impaction of faeces in the rectum presents with the picture of intestinal obstruction in the aged or bedridden patient. In all ages it is important to remember that acute appendicitis can mimic intestinal obstruction.

B. PARALYTIC OBSTRUCTION. This is usually called paralytic ileus—'ileus' being an alternative term meaning obstruction. It occurs temporarily after any abdominal operation and is a feature of shock, spinal injury and hypotension. Commonly it is due to peritonitis.

Fluid and Electrolyte Changes. In obstruction of the upper small bowel, fluids and electrolytes are lost because of vomiting. When the obstruction is lower down, there is stagnation in the distended bowel loops, normal absorption from the gut is interrupted, and the body is deprived of fluid even in the absence of vomiting.

Biochemically, there is haemoconcentration with loss of water and electrolytes, particularly chloride, sodium and potassium. Elderly patients may develop secondary renal failure and this will add to the electrolyte imbalance. A vicious circle develops as increasing obstruction raises the tension in the bowel and further diminishes absorption; then increasing electrolyte imbalance interferes with intestinal peristalsis rendering the obstruction more complete. Recovery is heralded by diuresis, signifying return of peristalsis and re-absorption of fluid from the lumen of the bowel.

Clinical Features. PAIN. In mechanical obstruction this is colicky and often originates at or about the site of the obstruction. It comes in waves and episodes of pain are accompanied by loud borborygmi. The advent of constant severe pain is indicative of strangulation.

Paralytic obstruction is associated with a dull constant pain in an abdomen which is ominously silent.

VOMITING. As already noted, this is copious in high obstructions and may be late or absent in obstructions of low small bowel or large bowel. The effortless trickle of foul-smelling fluid from the corner of the mouth of the lethargic patient is seen in untreated paralytic ileus, whereas in mechanical obstruction vomiting is projectile and intermittent.

DISTENSION. This may be absent or confined to some loops of the bowel which can be seen in the thin patient as ridges across the abdomen forming the so-called ladder pattern. Diffuse distension is late and often indicative of a large bowel obstruction.

CONSTIPATION. In complete obstruction, this is absolute, neither faeces nor flatus being passed. But in high obstructions, the bowels may continue to move unaided or with enemata, because of residual contents below the obstruction, while in large bowel obstruction, spurious diarrhoea may be due to an outpouring of faecal-stained mucus.

PHYSICAL EXAMINATION. The diagnosis of obstruction and its cause can usually be made on physical examination alone. The hernial orifices should be palpated for the presence of a tender irreducible swelling. In fat patients particular care must be taken to check the femoral regions.

The presence of scars from previous abdominal operations is noted. Distension, particularly of individual loops, is significant. A distended caecum may be both seen and felt in thin patients and immediately points to a large bowel cause. Tenderness anywhere in the abdomen is suggestive of peritoneal irritation and bowel strangulation. A palpable mass is associated with large bowel tumours and diverticular disease. A transient mass, felt perhaps during bouts of colic, indicates intussusception. Classically bowel sounds are increased and tinkling in mechanical obstructions, but in advanced cases they are infrequent and auscultation must be prolonged to detect the occasional tinkle. In paralytic ileus sounds are virtually absent.

Rectal examination usually reveals an empty ballooned rectum. In low obstructions there may be some blood and mucus. Obstruction due to carcinoma of the rectum is rare.

In cases of doubt, and for confirmation of the diagnosis, serial measurements of abdominal girth will detect progressive abdominal distension. A diagnostic enema will confirm the presence of obstruction, particularly if repeated washouts yield neither flatus nor faeces.

Radiology. Plain films of the abdomen, taken in the erect and supine positions, are most informative. The presence of fluid levels on the erect film, and of gas-distended loops on both films, show not only the diagnosis but also the site and probable cause of the obstruction.

Where the completeness of the obstruction is in doubt, serial films can be compared for any change in the gas patterns. Occasionally Gastrografin can be used to outline the bowel in the high obstruction, because the contrast medium will not be diluted at this level. Barium should be avoided lest it makes the obstruction worse.

Treatment. If intestinal obstruction is suspected, the opinion of a surgeon should be sought, even if non-operative measures are to be used.

The mainstays of treatment are decompression by gastrointestinal suction, the intravenous replacement of fluids and electrolytes, and operative relief of the obstruction. Urgent surgery is indicated for the relief of hernia and where there is strangulation. Correction of electrolyte deficiency must extend into the post-operative period, but in most cases of sudden onset the electrolyte upset is not marked.

In cases of more gradual development where there is a possibility that the obstruction can be relieved even temporarily, and in paralytic ileus, conservative measures assume greatest importance. Passage of a naso-gastric tube in an ill and nauseated patient requires skill and patience. Once in place, continuous suction with an electric pump, with periodic checks with a syringe to confirm that the tube is patent, will achieve upper intestinal decompression, and is as effective as intestinal intubation.

Intravenous infusion may require to be prolonged and biochemical estimations may be frequent, so that the veins should be treated with care. Frequent change of the site of infusion, using a fine needle of the butterfly type originally developed for scalp veins or infusion by a 'long-line' into the subclavian vein will reduce the incidence of phlebitis. Not only are fluids and electrolytes, with appropriate supplements of potassium, etc., required in accordance with biochemical findings, but where there has been blood loss, as in carcinoma of the bowel and diverticular disease, blood transfusion is required. Throughout conservative management, accurate fluid balance charts should be kept and daily totals recorded on an appropriate sheet to indicate gains and losses.

In those cases in which the obstruction relieves spontaneously, as in paralytic ileus and more especially in large bowel lesions, there may be an element of subsequent faecal impact in the rectum, so that periodic digital rectal examination should not be forgotten.

Peritonitis

Peritonitis is the reaction of the peritoneum to an irritant. Usually this is the result of infection, although sometimes the irritation is chemical at least initially, as when bile or duodenal contents leak into the peritoneal cavity. Appendicitis is one of the commonest causes of peritonitis in Britain and *Esch. coli* is the organism usually responsible.

Infection or chemical irritation cause the peritoneum to become congested and oedematous. There is an outpouring of fluid rich in antibodies and protein and containing large quantities of leucocytes. Dilution and destruction of the irritant is accompanied by its localisation by the formation of adhesions. Failure of these defence mechanisms is characterised by spread of the infection and by septicaemia and toxaemia. There is still a distressingly high mortality from generalised peritonitis.

Acute Peritonitis

In perforations, the onset is sudden, with severe abdominal pain, tenderness, rigidity and shock. The patient lies immobile, the respirations are short and grunting and the abdomen is retracted and motionless. These initial severe features then gradually decrease; the patient passes into a stage where he appears to have improved, and the diagnosis can be missed. Then, as paralytic ileus develops and fluid collects in the peritoneal cavity, there is increasing distension, the rigidity lessens, the tenderness remains and there are increasing signs of toxicity.

When peritonitis is secondary to inflammation of a viscus, such as appendicitis, the initial signs are those of the underlying disease, later to be replaced by the features of peritonitis. In advanced cases, only the history of onset remains to point to the probable cause.

Treatment. While the treatment of peritonitis is that of the cause, the ideal is its prevention. Thus acute appendicitis should be diagnosed before perforation and perforated peptic ulcer should be operated upon before the stage of chemical peritonitis is past.

Established peritonitis is treated by removal of the contaminating source when it is due to such conditions as appendicitis, perforation of hollow viscus or cholecystitis. Drainage of the abdomen, intravenous replacement of fluids and electrolytes, parenteral administration of wide spectrum antibiotics and the treatment of the concomitant ileus by naso-gastric suction form the basis of conservative and supportive management.

Prognosis. General peritonitis may resolve completely, but often it localises to form an abscess at the primary site, in the subphrenic region or in the pelvis. Persistence of fever, continued elevation of pulse rate, white blood count and ESR, and lack of general wellbeing should lead to efforts to locate such residual collections.

Pelvic Abscess

Usually resulting from localisation of a general peritonitis, a pelvic abscess forms in the lowest part of the peritoneal cavity, in front of the rectum and behind the bladder. In the female it is related anteriorly to the uterus and the posterior fornix of the vagina.

The abscess irritates the bladder causing frequency of micturition and the bowel causing diarrhoea with the passage of mucus and a feeling of incomplete emptying of the bowel. It is evident on rectal or vaginal examination as a tender mass.

Treatment is conservative as outlined above with, in addition, hot baths and douches. Discharge of the abscess rectally or vaginally is followed by rapid recovery.

Subphrenic Abscess

Localisation of pus between diaphragm and liver on the right side, or diaphragm, liver, spleen and stomach on the left, is a complication of peritonitis most commonly due to perforation of the stomach, duodenum or gall-bladder or to operation on these organs.

There are the general signs of persistent infection, evidence of chest infection and dullness at the base of the lung; there may be tenderness and slight oedema over the lower ribs posteriorly. Diagnosis is aided by X-ray of the diaphragmatic region which may show elevation of the diaphragm, a fluid level below it or changes in the lung above. Treatment is by surgical drainage.

Tuberculous Peritonitis

Although this condition is now rare in Britain, it is still relatively common in the Middle East, Africa and Asia. It is secondary to a tuberculous focus in the abdomen, usually in a mesenteric lymph node and it is characterised by wasting, malaise and abdominal distension. The abdomen contains fluid rich in protein from which tubercle bacilli may be cultured. Masses caused by matted omentum and loops of bowel may be palpable.

In the adult, the condition may be confused with advanced malignant disease and an unnecessarily hopeless prognosis given. Confirmation of the diagnosis may in some cases require laparotomy. The response to chemotherapy (p. 366) is good and often dramatic.

Acute Appendicitis

Though this condition is rightly regarded as surgical, it is of such importance as the most common cause of the 'acute abdomen' (p. 500) that it should be discussed in a textbook of medicine.

Aetiology. The disease occurs in both sexes and though it may develop at any age it is more common in young people. It is presumed that the rapid increase in the frequency of acute appendicitis since the turn of the century is connected with change in dietetic habits to a highly processed, low residue diet and a general adoption of a more sedentary existence. Acute appendicitis is generally obstructive, the lumen of the appendix being narrowed by swelling of lymphoid tissue in its wall, or by stricture from previous inflammation. Obstruction is made complete by impaction of a retained faecolith. Infection and distension lead to gangrene, perforation and peritonitis.

Clinical Features. The classical history is of the sudden onset of vague central abdominal pain followed in a few hours by shift of the pain to the right iliac fossa, where it becomes localised to McBurney's point. There is nausea and general malaise. There may be vomiting, but this is seldom severe and is often absent. In the early stages there is little elevation of temperature, so that rigors and a high temperature make the diagnosis of appendicitis unlikely. The pulse rate is increased, the tongue is furred and the breath foul.

Locally there is tenderness and guarding in the right iliac fossa, progressing to rigidity as peritonitis develops. Rectal examination should always be carried out, because it may disclose tenderness to the right.

The 'classical' history and findings account for less than 50 per cent of cases. The inflamed appendix may simulate many other diseases of the abdomen. In addition to pain, the patient may present with diarrhoea, with urinary symptoms, or with gynaecological complaints. On occasion acute cholecystitis or perforated peptic ulcer may be mimicked.

Differential Diagnosis. In children and adolescents *non-specific mesenteric lymphadenitis* may resemble appendicitis. This condition is probably due to a virus. It is characterised by vague abdominal pain, slight fever and a doughy sensation on abdominal palpation. There is ill-defined tenderness in the right iliac fossa. The distinction from appendicitis may be difficult and if in doubt it is safer to operate; otherwise treatment is conservative, recovery taking place gradually over a few weeks.

Treatment. The diseased appendix should be removed as early in the acute stage as possible. Attempts to temporise in the belief that mild forms of appendicitis can be distinguished from severe are dangerous, because the condition is notoriously deceptive. When there is obvious peritonitis, vigorous treatment with an antibiotic such as ampicillin given intramuscularly is indicated from the time of the operation for a period usually of some four of five days.

Only when a clearly defined appendix mass is present, without generalised abdominal signs, is a conservative policy allowable. Once the mass has subsided, probably within two to three weeks, the appendix should be removed. Not all patients presenting with an appendix mass require chemotherapy. Some need no more than rest, restriction of diet and the avoidance of purgatives. Others in whom there is more marked local tenderness, with low grade fever and general malaise, benefit from ampicillin given orally.

CHRONIC APPENDICITIS

At one time, this diagnosis was made, often in young women, to cover a multitude of chronic or recurring abdominal pains. Removal of the appendix failed to give relief because these patients were suffering from conditions such as the irritable bowel syndrome or dysmenorrhoea. Rarely chronic appendicitis is found in children in association with thread-worm infestation.

Tumours of the Small Intestine

Tumours of the small intestine are rare, although there is some evidence that lymphoma is more likely to develop in patients who have gluten-induced enteropathy. Simple tumours such as polyps and leiomyomas may cause chronic anaemia or intussusception or may be found unexpectedly in the course of radiological investigation or laparotomy.

Carcinoid Tumours

These arise from argentaffin cells and are usually seen in the appendix or ileum, although they may occur anywhere in the alimentary tract. These tumours produce a variety of substances including 5-hydroxytryptamine. When they originate in the small bowel, they may be multiple and usually spread to mesenteric glands and to the liver. The local effects of obstruction take second place to the general effects of flushing, diarrhoea and borborygmi brought about by the high levels of 5-hydroxytryptamine coming in part from the tumour, but mainly from its metastases. These systemic manifestations—the carcinoid syndrome—thus indicate spread of the disease, in spite of which long-term survival is possible.

Treatment. The primary tumour is usually removed whenever possible and particularly if it is causing obstruction. Metastases, too, can sometimes be excised, and hepatic lobectomy can be considered when spread appears localised to one lobe. Drugs for the control of flushing are generally unhelpful but diarrhoea can be reduced by parachlorophenylalanine.

DISEASES OF THE LARGE INTESTINE

Anatomy and Physiology

The main functions of the large bowel are the removal of water from the intestinal contents, the storage of faeces, and their evacuation at controlled intervals. Continence depends on training, on the function of a sphincter mechanism in the anal canal and on rectal sensation whereby the need to defaecate is appreciated.

The anal canal is sensitive to pain and touch, as is well demonstrated by the severe pain occasioned by fissures and inflamed piles. The rectum is insensitive to painful stimuli, so that the injection of a sclerosing agent for the treatment of haemorrhoids is painless. Rectal 'sensation' applies to an ability to appreciate distension and contraction.

Physical Examination

In thin subjects, the caecum, parts of the ascending colon, transverse colon and particularly the descending colon may be palpable and may be visible if distended. The presence of faeces, of tenderness, of thickening of the bowel wall, and of localised masses can be detected on palpation.

Digital examination of the rectum is an essential part of examination of the large bowel. With the patient in the left lateral position, the anus is inspected for fissuring, fistula, ulceration or haemorrhoids. Gentle introduction of the lubricated finger permits estimation of sphincter tone. Spasm and pain would indicate fissure in ano, laxity would lead to testing for rectal prolapse.

The lower part of the rectum, its contents and its surroundings can be palpated and the diagnosis of a variety of conditions particularly carcinoma can be made or confirmed. On withdrawal, the examining finger should be inspected for adherent blood or mucus. In the left lateral position, tumours within 10 cm of the anal margin may be felt and at a higher level if the patient strains down and forces the bowel towards the finger tip.

Endoscopy (p. 439), stool examination (p. 443), radiological investigation (p. 436) and motility studies (p. 442) are all important aids to diagnosis.

Ulcerative Colitis

Apart from the bacillary and amoebic dysenteries and tuberculous enterocolitis, there are certain non-specific chronic inflammatory bowel diseases which are associated with ulceration of the colon. One of these is Crohn's disease which may affect both the large and the small bowel; the other, commoner disease affecting the colon, is ulcerative colitis.

Aetiology. The aetiology of ulcerative colitis is not known. It is not due to simple infection, no specific organism having been identified from the faeces or the bowel wall. It is possible, however, that the disease is due to an abnormal immune response to faecal bacteria, since there is some evidence to suggest that antibodies formed to certain strains of *Esch. coli* may act as autoantigens to the colonic mucosa (p. 38). Further evidence in favour of an autoimmune process is the detection of anticolon antibodies in the serum of some patients with colitis. It has been suggested that hypersensitivity to certain foods, especially milk, may be a causative factor, and in practice temporary withdrawal of milk from the diet appears to improve diarrhoea in a few patients. However, the deleterious effects of milk in these patients could be due to lactose intolerance because of the development of secondary alactasia (p. 494) rather than to specific allergy to milk protein. Some authorities believe that psychological disturbances are responsible and claim that patients with colitis have a particular personality structure characterised by traits such as undue dependence on others, extreme sensitivity to personal slight and obsessive tendencies. It seems probable, however, that these traits are largely due to the disease process itself, since they disappear or greatly improve during a remission; indeed, one of the most rewarding effects of successful treatment is the remarkable improvement that may occur in the psychological well-being of the patient. Moreover, similar psychological features occur in patients with severe long-standing diarrhoea due to specific causes such as dysentery; nevertheless the patient and his physician may relate the attack or exacerbation to a recent stressful event. A familial tendency is suggested by the increased incidence of the disease amongst relatives of patients with colitis; the association between ulcerative colitis, ankylosing spondylitis and Crohn's disease has been mentioned earlier (p. 496).

Pathology. The rectum is always involved and the inflammatory process may be limited to this organ (proctitis). From the rectum the disease may spread to involve the distal colon (distal colitis) or the entire colon (total colitis). Whatever the extent of the disease, the inflammatory change is continuous throughout the affected part, in contrast to the patchy changes that occur in Crohn's disease of the colon. In the early stages the mucosa is swollen and reddened, and punctate bleeding points may be seen. As the disease progresses, ulceration involves the colon, and the ulcers may be quite superficial or may penetrate deeply, spreading longitudinally beneath the mucosa. In severe disease the mucosa may slough in parts to leave granulation tissue; the mucosa that remains becomes oedematous, hyperplastic and raised, giving the appearance of pseudopolyposis. In acute fulminant disease the bowel, especially the transverse colon, may be greatly dilated and the bowel wall becomes thin like paper and may rupture. In long-standing disease, the colon is shortened and generally narrowed with a lack of haustrations.

Microscopically, in contrast to Crohn's disease, the disease is characteristically confined to the mucosa which shows varying degrees of inflammatory change. In early colitis there is an increase in blood vessels and polymorphs and the lamina propria is oedematous. There may be collections of polymorphs in the lumen of the crypts which are termed 'crypt abscesses'. These may progress to destruction of the mucosa which is replaced by granulation tissue. Finally, on healing, the mucosa has a reduced number of crypts.

Clinical Features. The disease occurs most commonly between the ages of 20 and 40 years, but is seen at all ages. The clinical features and the management are largely determined by the extent to which the colon is involved, the severity of the inflammatory process, and the duration of the disease.

The principal symptom is diarrhoea with loose bloody stools containing mucus; defaecation is often accompanied by pain or lower abdominal discomfort, although severe pain is uncommon. Tenesmus may occur because of proctitis. Tenderness may be present on palpation of the colon, especially in the left iliac fossa; when peritoneal irritation is present, it signifies that the serosa is involved in the inflammatory process.

In severe ulcerative colitis, there is exhausting diarrhoea, fever, tachycardia and signs of dehydration. Toxic dilatation represents the most severe form. There is tachycardia, a high swinging temperature and abdominal distension. Untreated, the patient dies as a result of colonic perforation.

There is also a chronic stage of the disease in which the bowel is permanently damaged as a result of fibrosis. The colon in such cases behaves as a rigid tube incapable of absorbing fluid properly or of acting as a faecal reservoir. There is no toxaemia, but the patient lives in chronic ill-health and with persistent diarrhoea.

When the disease is confined to the rectum, the symptoms may be trivial if the inflammation is mild and consist of loose motions and perhaps blood-streaking of the stool. However, a severe proctitis will give tenesmus, frequent small and loose stools, together with bleeding per rectum, but systemic disturbance is absent. Paradoxically, when the disease is confined to the rectum and distal sigmoid (distal colitis) there may be constipation, with hard scybalous faeces and marked faecal retention on the right side of the colon.

Occasionally relapse can be associated with a period of emotional stress or intercurrent infection. There is no special risk during pregnancy, when indeed it is usual for the disease to remit, although if a relapse follows early in the puerperium it is nearly always severe.

Diagnosis. Although the diagnosis may be suggested by the history, sigmoidoscopy is essential for confirmation in most cases, but should not be performed in toxic dilatation which is diagnosed from the history, examination and straight X-ray of the abdomen.

The appearances of the mucosa depend on the severity of the disease. In proctocolitis of any severity, the mucosa appears engorged and hyperaemic and the normal vascular pattern is obliterated. In severe disease spontaneous bleeding will be seen; in less severe cases the mucosa appears intact, and bleeds only when it is gently rubbed, while in mild cases the only abnormality may be the absence of the normal vascular pattern.

Rectal biopsy is carried out to confirm the diagnosis and to exclude other causes of proctitis, such as Crohn's disease.

Radiology. While sigmoidoscopy confirms the diagnosis of ulcerative colitis, a barium enema examination demonstrates its extent. If only the rectum is affected, no abnormalities may be seen. When the disease is more extensive or severe, the various changes described under pathology can be seen, for example, shortening and narrowing of the colon and ulceration of the mucosa (Fig. 71). Often there is undermining of the mucosa ('collar-stud' ulcer), and the formation of pseudo-polypi.

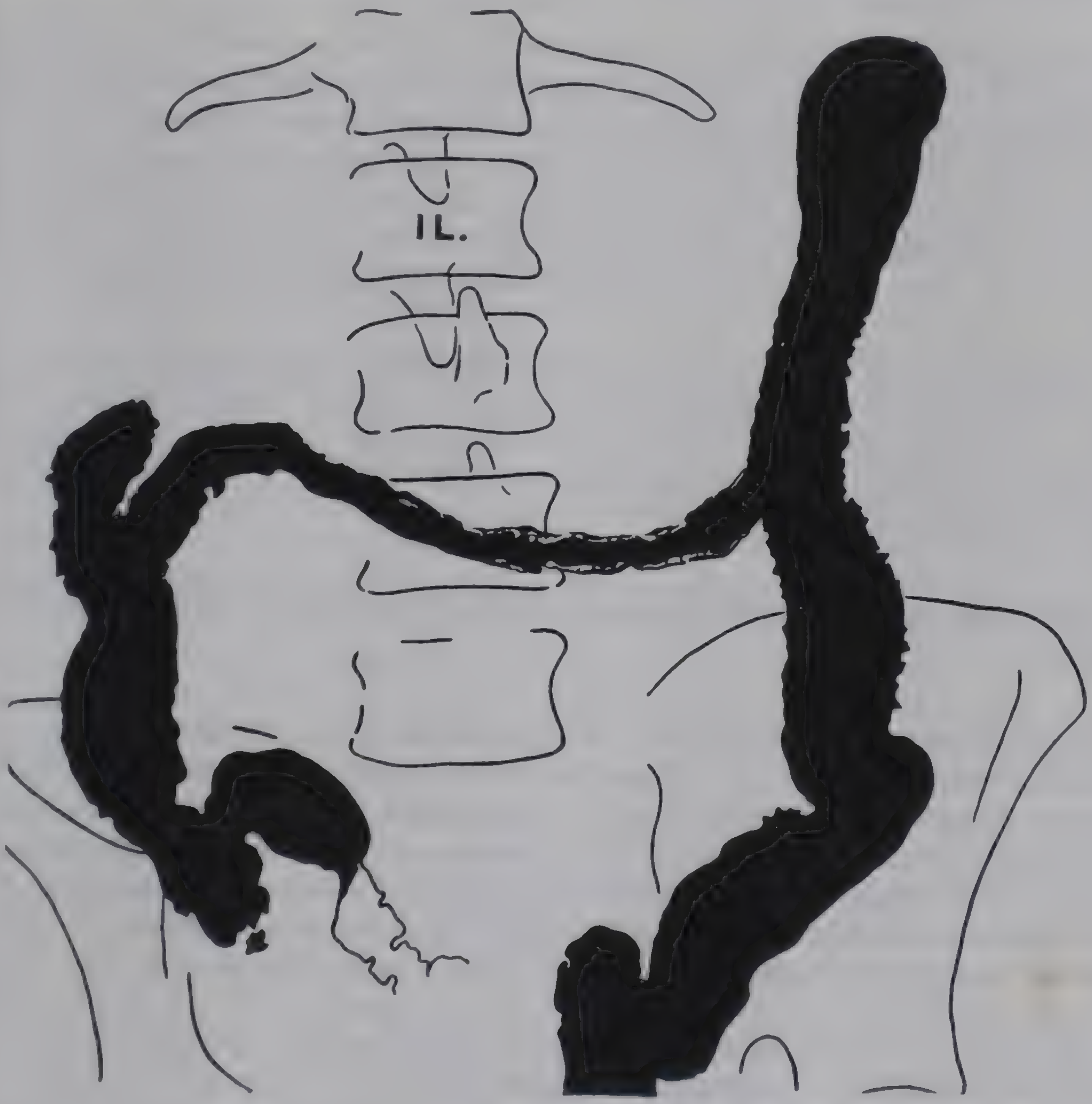


FIG. 71

Barium enema showing shortening and narrowing of colon with lack of haustrations and presence of numerous small ulcer craters giving a shaggy outline—generalised ulcerative colitis.

Barium enema examination should not be attempted in patients with severe colitis because of the risk of perforation. In these cases, plain films of the abdomen may allow a positive diagnosis to be made, since the colon will usually contain sufficient air to outline an abnormal mucosal pattern.

Laboratory Investigations. The patient is often anaemic and there may be leucocytosis and a raised ESR. In severe cases there are electrolyte disturbances and protein loss from the colon may lead to hypo-albuminaemia.

Sometimes the liver function tests are abnormal. The stool is cultured for pathogenic bacteria and a search is made for amoebae to exclude an infective cause for the colitis. Proctitis can occasionally be due to gonorrhoea. Blood cultures are required if septicaemia is suspected.

Complications. INTESTINAL STRICTURE. In the chronic forms of the disease, stricture may occur at any level in the colon, but usually in the anal canal.

CARCINOMA OF THE COLON. Carcinoma of the colon develops much more often in patients with long-standing ulcerative colitis than it does in the normal population, the risk being related to the duration, extent and age at onset of the disease. The risk increases greatly after the disease has been present for ten years or more. It is greatest in patients with total colitis who develop the disease under the age of 20 years; in this group the risk of cancer of the colon is about 40 times greater than it is in a comparable normal population.

SYSTEMIC COMPLICATIONS. These include arthropathy affecting principally the large joints, ankylosing spondylitis, lesions of the eye (especially iritis), skin lesions and liver disease. As in Crohn's disease the relationship between the systemic manifestations and the bowel disease is not clear. Septicaemia may occur in severely ill patients.

Treatment. Management differs according to the severity and extent of the disease.

GENERAL MEASURES. Admission to hospital is required for patients with severe bowel symptoms, especially when there are general systemic disturbances such as weight loss, anaemia, fever or tachycardia. Such patients may require intense supportive treatment until the disease remits or as a preparation for surgery. The measures should include correction of dehydration and electrolyte deficiencies, especially hypokalaemia, blood and plasma infusions to correct anaemia and hypoproteinaemia, and a high protein, low residue diet. Blood cultures should always be taken initially and be repeated throughout the course of the illness if fever persists; Gram-negative bacteria are the commonest organisms involved; if septicaemia is suspected parenteral administration of broad spectrum antibiotics is necessary (p. 106). However, antibiotics have no special place in the primary management of colitis. Moniliasis of the mouth and upper pharynx is common, especially in severely ill patients on corticosteroids, so the mouth should be inspected regularly and swabs taken for culture if moniliasis is suspected. Treatment is with nystatin (p. 104).

There is no satisfactory drug for controlling diarrhoea. Codeine phosphate, 30-60 mg three- to six-hourly, is of some value, but may produce nausea; alternatively, an anticholinergic such as propantheline may be prescribed. However, all these drugs should probably be avoided in severely ill patients since they may precipitate an attack of toxic dilatation.

Almost all patients with severe colitis show some anxiety and agitation and they benefit from tranquillisers.

ANTI-INFLAMMATORY DRUGS. 1. *Corticosteroids.* Although there is no specific treatment for ulcerative colitis, the introduction of corticosteroids and corticotrophin has greatly improved the outlook.

(a) *Local Treatment.* When the disease is confined to the distal colon or the rectum, symptoms may be limited to moderate diarrhoea (three or four stools per day) with the passage of blood from time to time, while general health is maintained. Such patients may be treated by administration of corticosteroids as suppositories when there is local rectal involvement, or as self-administered enemas if the distal colon is involved. The preparations commonly used are prednisolone-21-phosphate or betamethasone, and both are available in disposable enema form. The patient is taught to administer the enema himself, twice daily, retaining the material for as long as possible; suppositories may be inserted twice or three times daily for the treatment of proctitis. Either form of treatment may be continued for several weeks, the duration being judged by the sigmoidoscopic appearances.

(b) *Systemic Treatment.* Of the various corticosteroids available prednisone or prednisolone are the preparations most commonly used. These are given in doses of between 20-60 mg daily by mouth for three to six weeks depending on response. The usual contraindications to the use of these drugs must be observed (p. 670) and supplements of potassium salts should be given (p. 191). Used in this way, the corticosteroids will induce remission in the majority of patients, the dose being reduced at weekly intervals as improvement takes place. The corticosteroids give rise to a sense of well-being in the patient and in addition improve appetite, so that the problem of persuading the patient to eat sufficient food is often solved. The beneficial effects of corticosteroid therapy have been established as a result of careful clinical trials; the evidence suggests that they are more effective in a first attack of ulcerative colitis, whereas corticotrophin may be more beneficial in the treatment of relapse. A long-acting form of corticotrophin (e.g. tetracosactrin zinc phosphate complex) should be used, and given in doses of the order of 1 mg daily by intramuscular or subcutaneous injection. This dosage is continued for a week after symptoms have remitted and it is then reduced at weekly intervals as in the case of corticosteroids. For convenience oral corticosteroids may be substituted once the patient has responded adequately.

2. *Sulphasalazine.* This sulphonamide derivative is also used in the treatment of ulcerative colitis, but is less effective than the corticosteroids. It has the disadvantage of inducing nausea, vomiting and skin rashes; occasionally it induces blood dyscrasias. Its use is generally restricted to the management of mild or moderately severe colitis and in the prevention of relapses once corticosteroids have controlled the disease; under these circumstances it is prescribed at dose levels of 3-4 g daily, the dose being reduced gradually depending on response.

IMMUNO-SUPPRESSIVE THERAPY. Because ulcerative colitis has been shown to be associated with autoimmune reactions, treatment of the disease by immuno-suppressive drugs such as azathioprine (p. 40) would seem logical. Such a method of management is still under trial and it is not yet possible to say whether the advantages outweigh the disadvantages.

SURGICAL TREATMENT. If the appropriate medical measures are carried out assiduously, the majority of patients with proctitis or moderately severe colitis will pass into remission. In severe forms of ulcerative colitis, where there is toxic dilatation of the colon or perforation and in the occasional patient with severe haemorrhage, emergency surgical treatment is required. Usually it takes the form of colectomy with ileostomy, the rectum and distal colon being removed at a later stage when the crisis is over.

Acute ulcerative colitis which fails to respond to medical treatment, or which relapses in spite of adequate treatment, is an indication for procto-colectomy. This is also indicated in chronic forms, where the disease burns out but leaves a permanently damaged bowel, perhaps with stricture formation. Long-standing disease, particularly when the onset has been in childhood, carries a risk of carcinoma and accordingly total bowel involvement, with activity extending over more than 10 years, should lead to surgery.

At all stages of the disease, the timing of and preparation for surgery are important and require a joint medical and surgical approach. In emergency situations, intensive pre-operative replacement of blood, fluid and electrolytes is needed and operation is commenced as soon as the patient is fit to withstand surgery. In less urgent situations, the moment for surgery depends on the degree of improvement in the patient's general condition to be expected from pre-operative medical measures. The aim is to get the patient into the best possible condition, the art being to avoid the need to operate in a deteriorating position.

Operation usually implies total procto-colectomy with a permanent ileostomy. Whenever possible, in addition to a full explanation of ileostomy and its management, with a demonstration of the actual appliance to be used, the patient should have the opportunity before operation of meeting someone with an established ileostomy. Modern surgical techniques and the range of ileostomy appliances available make for easy management of the stoma and allow the patient to live an almost normal life with little restriction of physical activity. To be kept in touch with advances in technique of ileostomy care, he should join an ileostomy association or be enrolled in a stoma therapy clinic.

Prognosis. It is extremely difficult to give a prognosis in ulcerative colitis. The extent of involvement of the colon is an important consideration, the outlook being very much better, for example, if only the rectum is involved. The immediate death rate in patients with fulminating disease, however treated, is not less than 40 per cent, and it is high also in patients developing an attack over the age of 60. In general, the overall mortality from ulcerative colitis is of the order of 10 per cent, but this figure can be very greatly reduced when the patient is treated by those with special experience of the disease. Thus, the mortality from total procto-colectomy done during a remission by an experienced surgeon is about 2 per cent, whereas mortality for procto-colectomy done as an emergency procedure is 10 per cent in the best hands, and may be 20 per cent or 30 per cent in those with little experience of the disease. Attention has been drawn to the risk of carcinoma in long standing cases.

Diverticular Disease

DIVERTICULOSIS AND DIVERTICULITIS

Though diverticula occur throughout the gastrointestinal tract, they are most common in the large bowel. The presence of diverticula is known as diverticulosis; when they are inflamed the condition is known as diverticulitis. Such inflammation occurs almost exclusively in colonic diverticula. Because it is often difficult to separate the two conditions on clinical or radiological evidence, they are usually grouped together under the term ‘diverticular disease’.

Aetiology. In theory diverticular formation in the colon could be explained by weakening of the bowel wall or by increased intraluminal pressure. In diverticulosis the muscular coat of the bowel is often greatly thickened, suggesting that the diverticula have formed as a result of increased intracolonic pressure. Manometric measurements support this view. It can be shown that pressure in the bowel is high and that there is an area of spasm or failure to relax at the pelvirectal junction, but the exact factors responsible for the increased pressure and spasm are not known.

The condition occurs especially in middle-aged or elderly subjects and affects males and females equally. It is rare in Africa and Asia, leading to the suggestion that the low residue, high carbohydrate diets common in affluent countries, together with the use of purgatives, may be responsible for the development of diverticular disease.

Pathology. The pelvic colon is most commonly involved. Its muscle wall is thickened but the diverticula themselves are pouchings of the mucosa and have no muscle coat. It is not clear how they become inflamed. Radiological examination frequently shows the presence of a faecolith in a diverticulum, and it may be that faeces collect because of the inability of the diverticulum to contract. An area of inflammation may develop in the diverticulum and whilst this may resolve, it may become acute with perforation, local abscess formation, fistula and peritonitis. When there are repeated attacks of diverticulitis, the bowel wall becomes progressively thickened with narrowing of the lumen leading eventually to large bowel obstruction.

Clinical Features. Pain or discomfort felt in the left iliac fossa is a common complaint and there may be associated local tenderness. Change of bowel habit, either of increasing constipation or constipation alternating with diarrhoea, is frequent. This is the most important symptom of colonic disease and can occur with any lesion. By middle age, bowel habits are firmly established and a definite alteration usually betokens organic disease in the colon such as carcinoma or diverticulitis and always calls for complete investigation. Severe rectal bleeding may be the first sign of diverticular disease in a patient with no preceding bowel disorder.

Acute diverticulitis can give rise to a clinical picture of the acute abdomen, with severe pain, guarding and rigidity on the left side, the signs of peritonitis and obstruction being combined.

In the chronic forms, there may be symptoms of subacute obstruction with increasing abdominal distension, borborygmi and colicky pain. Urinary symptoms of frequency and dysuria may be present. Occasionally a fistula to the bladder gives rise to pneumaturia and faecal contamination of the urine.

On examination, the thickened tender colon may be palpable in the left iliac fossa. A mass may be present in those patients who have developed diverticulitis, with or without abscess.

Rectal examination and sigmoidoscopy are of no value in making the diagnosis of diverticular disease, but are essential to exclude cancer of the rectum and pelvirectal junction. Both conditions may co-exist in an age group which is liable to both, or one may mimic the other to the extent that even at operation the true diagnosis is uncertain.

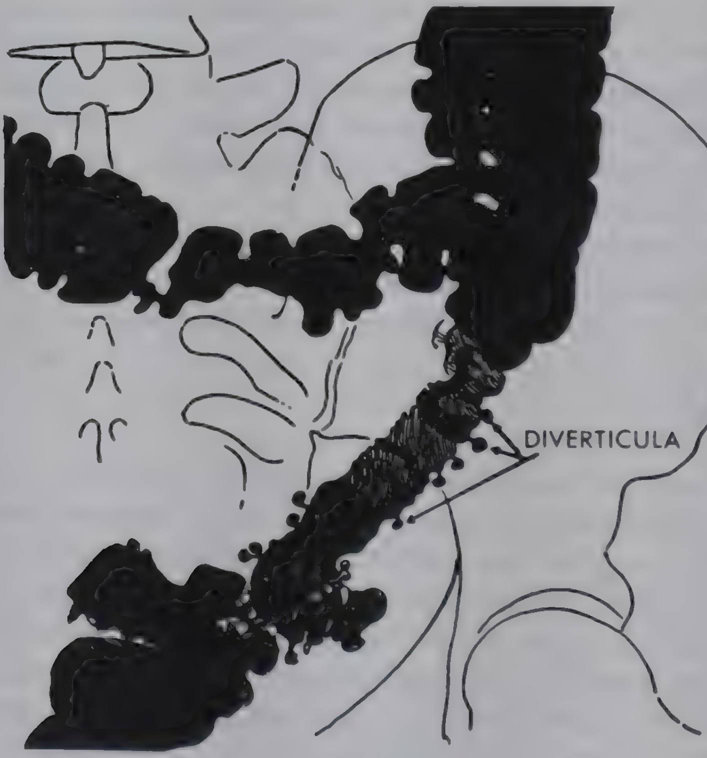


FIG. 72

Barium enema showing numerous diverticula with general narrowing and irregularity in descending and pelvic colon—diverticular disease.

Radiology. Radiological examination is the most valuable diagnostic procedure. Diverticulosis produces a characteristic picture in which the sacs are outlined as pouchings from the main contour of the gut (Fig. 72). If a faecolith is present in the diverticulum, the barium partially surrounds it in a crescentic fashion. When a barium enema is evacuated, barium is frequently left behind in the diverticula which are clearly outlined. If diverticulitis is present, there will be narrowing, rigidity and lack of normal haustration of a segment of colon. Whether or not there are diverticula present, the main diagnostic difficulty is to distinguish the appearances from those of carcinoma and the distinction may be impossible.

Treatment. Asymptomatic diverticulosis is common, is often found accidentally and requires no treatment. Patients who have mild or moderate symptoms will be relieved by regulation of the bowel. A diet with plenty of roughage in the form of vegetables, fruit, or bran is usually sufficient. If not, the taking of a bulk producer such as Isogel or Normacol Special can be recommended. Strong purgatives should be avoided.

During an attack of acute diverticulitis, bed rest, antibiotics, fluids intravenously and orally, or even cessation of feeding with naso-gastric suction may be required. Most severe attacks subside spontaneously but a few require emergency surgery which will probably be confined to a temporary defunctioning proximal colostomy, to be followed later by local resection. An emergency partial colectomy may be required for acute bleeding.

Elective surgery is indicated, after recovery from an acute attack, in patients who develop obstructive features, who have complications such as fistula and those in whom the possibility of carcinoma cannot be excluded. The treatment of choice is resection of the involved segment of pelvic colon with primary anastomosis.

A few patients fail to respond adequately to medical treatment and of these some will be considered for surgery. This may take the form of resection, or of myotomy of the pelvic colon loop. In patients without advanced fibrotic changes the latter procedure gives good results but its long term efficacy has still to be established.

Carcinoma of the Colon and Rectum

In Britain, carcinoma of the large intestine is the most common malignant tumour of the alimentary tract. In contrast it is rare in Africa and Asia.

Aetiology. As elsewhere in the body, search has been made for a precancerous condition. The only diseases known to be clearly associated with cancer are long-standing ulcerative colitis and familial multiple polyposis. There is no established association between carcinoma and diverticular disease. It is a disease of advancing years, affecting males more than females.

Pathology. In two-thirds of patients, cancer of the large bowel occurs in the left colon or rectum. Multiple tumours are present in 2 per cent of cases. Macroscopically the tumour may be proliferative and fungating, ulcerative and infiltrating, polypoidal or encircling as a 'string' stricture.

Spread occurs directly in and through the bowel wall, by lymphatics and by the blood stream through both portal and systemic circulations. Colon carcinoma is capable of direct implantation on exposed surfaces, such as a suture line or area of trauma in the bowel. The liver is the organ most commonly involved in metastases.

Clinical Features. Symptoms vary depending on the site of the carcinoma. In tumours of the left colon, obstruction is early. Tumours of the right colon present with anaemia, cachexia and bowel upset, but obstruction is late because of the relatively fluid nature of the bowel contents. As a consequence left-sided tumours tend to be diagnosed earlier.

Change in bowel habit, anaemia, weight loss and sometimes excessive borborygmi, abdominal distension and griping pains indicating subacute obstruction, all point to a large bowel tumour. Some, however, are relatively symptomless until the patient presents as an emergency with obstruction.

Carcinoma of the rectum causes early bleeding with mucus discharge and later a feeling of incomplete emptying of the bowel. Obstruction is a feature of tumours of the pelvirectal junction but not the rectum proper, which is capacious and distensible.

Rectal examination must never be omitted. Occult blood is found in the stool if an ulcerating lesion is present.

Overall, the findings on physical examination range from no obvious abnormality, to the signs of advanced malignancy.

Endoscopy. More than 50 per cent of malignant tumours of the large bowel occur in a part accessible to direct inspection with the sigmoidoscope, i.e. the rectum and the lower pelvic colon. With the colonoscope the whole left side of the bowel at least can be inspected, thus bringing into range 75 per cent of all tumours.

Endoscopy, after suitable preparation of the bowel, should always be carried out. The whole or part of a growth may be seen and a biopsy specimen removed. Even when direct vision is impossible, there may be tell-tale evidence of blood and mucus in the lumen. The examination may need to be repeated if the initial biopsy report is negative. In rectal carcinoma histological proof should always be obtained before resection. Laparotomy may be required to establish a diagnosis of carcinoma of the colon.

Radiology. Barium enema is a more useful method of examination for diseases of the colon than the 'follow-through' of a barium meal, though the latter may be satisfactory for examination of the ascending colon. The caecum and the rectum are difficult to examine radiologically and diagnosis in the former may depend on laparotomy, while in the latter reliance should be placed on endoscopy. The usual radiological appearances of a carcinoma are either those of a stricture or a filling defect in the barium outline (Fig. 73).

Diagnosis. There are no pathognomonic signs of carcinoma of the bowel. Perpetual vigilance is needed and the possibility of carcinoma should be remembered when anyone of middle age presents with rectal bleeding, change of bowel habit or iron deficiency anaemia. The doctor who makes a diagnosis of piles without rectal examination, or of constipation uncritically in a middle aged person, accepts a grave responsibility.

Treatment. The treatment of choice is resection of the tumour as a one-stage procedure. If there is no colonic obstruction, or if it can be overcome by enemata, time should be spent in preparing the bowel by washouts and antibiotics and anaemia should be corrected where necessary by pre-operative transfusion.

Carcinoma of the rectum will require total removal of the rectum with permanent colostomy and for this the patient requires pre-operative introduction to colostomy and its management (p. 514).

In general the outlook of surgery for carcinoma of the large bowel is good, but success depends on early diagnosis and operation before spread has occurred and before obstruction renders the surgeon's task more complicated.

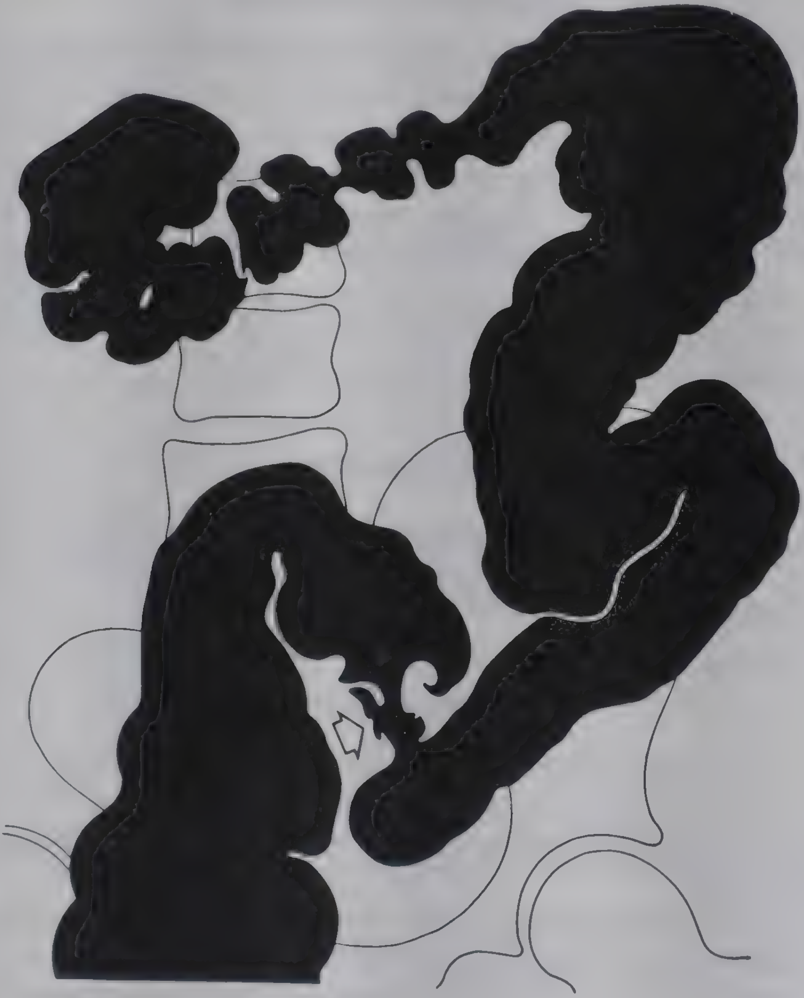


FIG. 73

Barium enema showing, at arrow, localised narrowing in sigmoid colon due to a carcinoma.

Benign Tumours of the Large Intestine

Various benign tumours of the large intestine occur, but only polyps are found with any frequency. These tumours may be single or multiple and are most commonly found in the left side of the colon. They are round and on a stalk, which may lengthen so that the tumour can move up and down the lumen of the bowel. These tumours may be found coincidentally at operation or on barium enema, or they may cause bleeding, discharge of mucus, or intussusception. Occasionally, because of their mobility, these tumours may prolapse through the anus to appear as a red cherry-like mass.

Although they are benign and adenomatous, polyps of the large bowel may become malignant. The malignant change may not extend into the stalk, so that removal of the polyp and stalk may suffice. It follows that polyps should be treated seriously and removed and that the stalk as well as the polyp itself should be examined histologically. In general polyps of more than 1 cm in diameter are probably malignant.

Multiple Polyposis

In this condition, transmitted by autosomal dominant inheritance, there may be thousands of small polyps diffusely scattered over the mucosal surface of the colon and rectum. They appear at adolescence and turn malignant in about 15 years, the patient often dying from carcinomatosis before the age of 40. The disease can be recognised by routine examination from adolescence onwards of members of affected families. Prevention of carcinoma means removal of the colon and rectum with permanent ileostomy, although symptomless members of the family may find ileo-rectal anastomosis with diathermy removal of rectal polyps and periodic surveillance more acceptable.

Megacolon

Megacolon is a condition characterised by dilatation of the colon and obstinate constipation. The disease may be separated into two groups, congenital, or Hirschsprung's disease proper, and acquired megacolon.

Hirschsprung's Disease

The cause is a congenital absence of the myenteric nerve plexus in the wall of the pelvic colon and upper rectum. Occasionally the defect extends proximally. A similar defect is seen in Chagas' disease where the ganglia are destroyed by a trypanosome (p. 974).

Boys are often more affected than girls and symptoms of constipation, abdominal distension and vomiting date from birth. They may come in attacks, but even between attacks there is persistent pot-belly. The rectum is empty on digital examination.

Radiological examination with small amounts of barium show a small rectum, a narrow segment above and then proximally wide dilatation of the colon full of retained faeces. The diagnosis can be confirmed by rectal biopsy of sufficient thickness to include muscle of the bowel wall.

Treatment. Treatment is surgical and the abnormal segment of colon and rectum is excised. In the newborn, preliminary colostomy may be required to allow normal development and to prevent the complications of enteritis and respiratory infection.

Acquired Megacolon

In this group of cases, there is no defined aetiology and no defined age-group. Some are examples of a milder, short segment form of Hirschsprung's disease.

Some are associated with an endocrine disturbance as in cretinism, or with the abuse of drugs, such as chlorpromazine, or are thought to be of psychogenic origin. The condition is seen among inmates of mental hospitals. Chagas' disease has cast a new light on the aetiology of megacolon.

Radiologically, acquired megacolon usually shows no narrowed segment, the dilatation instead extending down to the anus. The rectum is full of faeces.

Most cases can be managed conservatively, by treatment of the cause where identifiable, by high residue diets, laxatives and perhaps colonic washouts. In a few patients colon resection has been used as a last resort in the relief of obstinate constipation.

INFECTIONS OF THE ALIMENTARY TRACT

Infections of the mouth due to thrush and other organisms are discussed on page 445, and gastroenteritis caused by bacterial food poisoning on page 71. Epidemics of acute but transient gastroenteritis may be caused by Echo, Coxsackie and other viruses. Usually identification of the viral nature of the infection is not possible and diagnosis is presumptive when no bacterial cause has been demonstrated.

The small intestine is involved in typhoid and paratyphoid fevers (p. 69), cholera (p. 974) and staphylococcal enterocolitis (p. 63). Tuberculous ileitis is now rarely encountered in Britain.

The principal infections involving the large intestine are bacillary dysentery (p. 74) and amoebic dysentery (p. 970).

VASCULAR DISORDERS OF THE ALIMENTARY TRACT

Vascular disorders of the alimentary tract usually occur in elderly patients with other evidence of degenerative vascular changes or in patients with heart disease or arrhythmias.

Superior Mesenteric Artery Occlusion

Sudden severe abdominal pain, vomiting and watery diarrhoea form the classical triad of initial symptoms in this condition. The cause is either thrombosis of the superior mesenteric artery secondary to atherosclerosis, or embolism often associated with atrial fibrillation.

Clinical diagnosis is difficult and tends to be delayed until gangrene of the bowel and peritonitis have developed. By then the outcome is almost always fatal. Diagnosis in the first few hours offers the possibility of restoration of the blood supply to the bowel by embolectomy, endarterectomy or arterial bypass.

Early diagnosis is facilitated by emergency aortography to outline the origin and course of the superior mesenteric artery.

Inferior Mesenteric Artery Occlusion

Atheroma with secondary thrombosis or embolism lodging in the inferior mesenteric artery imperils the viability of the pelvic and descending colon.

The clinical picture is less severe than that of superior mesenteric artery occlusion. Diagnosis may be made at laparotomy for what is thought to be diverticular disease or volvulus, and treatment is left hemicolectomy.

Chronic Ischaemia

With the greater use of angiography, the symptoms of chronic ischaemia of the bowel are becoming recognised. Pain, brought on by meals (abdominal angina) malabsorption, disturbance of bowel function and stricture formation are some of the modes of presentation. In the large bowel, in the region of the splenic flexure where superior and inferior mesenteric blood flows anastomose, ischaemic stricture is most commonly seen and may be first recognised in the course of a barium enema.

Ischaemic colitis may be acute or chronic, widespread or localised. In approximately 50 per cent of older patients no underlying cause is detected, although in patients under the age of 50, a predisposing factor is usually identifiable.

Unless gangrene develops, treatment is conservative in the acute stage, by drip, suction, bed rest and antibiotics.

PSYCHOGENIC DISORDERS OF THE DIGESTIVE SYSTEM

Disorders of the digestive system due to psychological factors are common and they may mimic organic disease. Stress may be associated with a symptom such as dyspepsia ('indigestion'), abdominal discomfort or diarrhoea. The precise mechanisms by which psychological disturbances produce alimentary symptoms is uncertain. However, it is known both from direct and indirect observations that gastrointestinal functions such as gastric secretion, alimentary motility and blood flow can alter with change in emotion or mood.

Patients with anxiety states may develop a wide range of alimentary symptoms such as dryness of the mouth, a feeling of a lump in the throat (globus hystericus), anorexia, nausea, vomiting, abdominal discomfort, aerophagy with belching, abdominal pain, diarrhoea or constipation. Patients with a depressive illness may have similar complaints, notably anorexia, a bad taste in the mouth, nausea and vomiting especially in the morning, and constipation. Any or all of these symptoms may be due to organic disease and it should never be forgotten that the patient with an anxiety or depressive illness may also have an organic lesion such as peptic ulceration or alimentary carcinoma.

A careful history will usually identify complaints of psychological origin; pain of this type may have no discernible pattern with no clear time or food relationships and the patient often has difficulty in describing it. The more bizarre the description, the less likely is the symptom to be organic in origin.

The sympathetic physician will encourage the patient to express his underlying anxieties and fears; once these are brought to the surface the patient, and the clinician, recognise the relationship between the somatic symptoms and the emotional state.

Occasionally the physical examination will reveal a manifestation of anxiety state such as inappropriate sweating or tachycardia. If abdominal tenderness is elicited, this is often quite disproportionate both to the patient's physical well-being and to his complaint. Although it is often necessary first to exclude organic disease by physical examination and appropriate investigation, positive evidence must also be sought regarding the patient's psychological state.

While anxiety neurosis and depression are most commonly encountered, certain syndromes, primarily psychogenic but with a specific alimentary disturbance, merit separate description. These are anorexia nervosa, globus hystericus, nervous dyspepsia, psychogenic vomiting and the irritable bowel syndrome.

Anorexia Nervosa

Anorexia is a common symptom of anxiety neurosis; it may be severe in depressive states, and is sometimes a troublesome feature of psychotic illnesses. The term 'anorexia nervosa' refers to a serious disorder in young women characterised by a refusal to eat sufficient food, severe weight loss and amenorrhoea. The patient may go to extreme lengths to evade taking food or to conceal food which she is supposed to have consumed at the table and which is afterwards thrown away. Food that has been eaten under observation may be rejected afterwards by self-induced vomiting The psychopathology of the condition is discussed on page 925. Management is best conducted in hospital under the joint supervision of psychiatrist and physician.

Globus Hystericus

Some patients complain of a feeling of a lump in the pharynx, frequently described as difficulty in swallowing. On questioning, however, it becomes clear that the sensation actually occurs between meals, rather than during the act of swallowing so that there is no true dysphagia. The symptom occurs most frequently in tense, anxious individuals, and is probably related to a heightened awareness of the act of swallowing saliva. Before accepting that the symptom is psychological in origin it is necessary to exclude a structural lesion in the upper pharynx by barium swallow and meal examination and if necessary by endoscopy. Occasionally a web in sideropenic dysphagia will be responsible for the symptom (p. 449).

Psychogenic Dyspepsia

This term is used to describe a condition in which epigastric discomfort, a feeling of undue satiety after eating, occasional anorexia, nausea or vomiting and a complaint of excessive 'wind' are associated with psychoneurotic features such as anxiety, irritability, or a feeling of tension. Other somatic symptoms include attacks of sweating or tachycardia, or a sense of weakness. Sometimes the principal feature is pain and the history may bear superficial resemblance to that obtained in peptic ulcer; however the pain is diffuse rather than localised, is often described in bizarre terms, and has no relationship to food or time. The symptoms may have been present for months or years. The diagnosis can often be suspected both because the symptoms are not compatible with organic disease and because of evidence of psychoneurosis. However, organic disease should be excluded by appropriate investigations and frequently symptoms are relieved after the reassurance that barium meal or endoscopy is negative. The extent to which investigation should be carried out is a matter for clinical judgement. For example, the early symptoms of an organic lesion such as peptic ulcer may themselves precipitate a mild anxiety state which in turn overshadows the original symptoms; the early symptoms of a gastric carcinoma are characteristically vague, and dyspepsia in the middle-aged should never be attributed to neurosis without full investigation. On the other hand unnecessary investigation may consolidate the psychological difficulties of inadequate, over-dependent personalities, some of whom, consciously or unconsciously, may be manipulating the doctor.

Treatment. The exclusion of organic disease is an important part of the management because it allows the physician to reassure the patient with confidence. The psychological origin of the symptoms should be explained to the patient sympathetically. The condition may be helped by drugs such as diazepam or dicyclomine. The patient is encouraged to eat in a calm and relaxed atmosphere. Frequently, such patients recognise that they have a 'weak' stomach which bears the brunt of recurrent stress but they may come to a doctor for reassurance from time to time. Sometimes a patient with obsessive tendencies discovers some private ritual or diet to which he attaches great importance. Provided such a diet is harmless and does not exclude essential foodstuffs it can be left unaltered.

Psychogenic Vomiting

This is not an uncommon manifestation of anxiety states and it occurs usually on wakening, or immediately after breakfast; only rarely does it occur later in the day. It is probably a reaction to awakening and facing up to the worries of everyday life; in the young it can occur as a school phobia. There may be retching alone or the vomiting of gastric secretions or food. Although psychogenic vomiting may occur regularly over long periods, there is little or no weight loss and this is of value in distinguishing it from vomiting due to organic disease of the alimentary tract; another helpful feature is that psychogenic vomiting is rarely preceded by excess salivation. Early morning vomiting may also occur in depressive illnesses and in the early months of pregnancy.

It is essential in all cases to assess and, if possible, alleviate the underlying psychological disturbance. Tranquillisers and antiemetic drugs (e.g. prochlorperazine 5-10 mg thrice daily) have only a secondary part to play.

The Irritable Bowel Syndrome

One of the commonest disorders of the alimentary tract is that of long-standing colonic dysfunction associated with abdominal pain and for which no organic cause can be found. Bowel habit is disturbed by diarrhoea or constipation occurring alone, or alternating one with the other. Because mucus is sometimes recognised in the stool, the disorder used to be called mucous colitis; this latter term is quite inappropriate since there is no question of inflammation of the colon, the excess of mucus being associated simply with the underlying motility disorder. Other terms used for the disorder are spastic colon and nervous diarrhoea.

Aetiology. Manometric studies from the distal colon (p. 442) have shown various patterns. When constipation and pain are the predominant symptoms, intraluminal pressure is usually increased and there is an increased frequency of pressure waves, whereas motor activity is often reduced in patients with painless diarrhoea; the motility of the small intestine may be disturbed also. These changes in intestinal motility are not constant, and may not be detectable when the patient is symptom-free. Motility studies are not of value for diagnostic purposes.

The cause of these disturbances is not known and several factors may be involved. Psychological disturbances, especially anxiety, are frequent and patients with the condition generally tend to be tense, conscientious individuals who worry excessively about family or financial affairs. Many patients relate the onset of their symptoms to an attack of infective diarrhoea such as dysentery, or food poisoning. Some patients seem obsessed with bowel function and have taken purgatives regularly in the past to ensure regular defaecation. Individual attacks, especially of diarrhoea, are often attributed by the patient to special foods such as fruits, salads and fried food.

Clinical Features. The syndrome occurs more commonly in women than in men, usually between the ages of 20 and 40 years. The commonest symptom is abdominal pain, occurring in attacks and referred to the left or right iliac fossa or to the hypogastrium; it may be continuous or colicky, diffuse or localised and is rarely severe. It is generally relieved by defaecation and is sometimes provoked by food. In some patients pain is associated solely with constipation, the stools being hard and pellet-like and accompanied by mucus. In other patients occasional bouts of diarrhoea are interspersed by periods of constipation when purgatives may be taken which precipitate another episode of diarrhoea, leading to a vicious cycle. Some patients complain of intermittent painless diarrhoea, passing several loose or watery stools daily during an attack. Diarrhoea occurs characteristically during the morning, either before or immediately after breakfast and it almost never occurs during the night. Defaecation is often precipitate especially after meals, presumably due to an exaggerated gastrocolic reflex.

Other symptoms include abdominal distension, especially after meals and an awareness of intestinal peristalsis ('rumblings') or audible borborygmi.

Nausea, anorexia and complaints of tiredness and weakness occur, especially during attacks of diarrhoea. Vomiting is uncommon.

The patient may appear tense and anxious, but seems well otherwise. Abdominal tenderness is common, especially over the right or left parts of the colon, and the pelvic colon may be contracted and pencil-thin on palpation in the left iliac fossa. There is no rigidity or evidence of peritonism. About one-third of patients show the scar of an appendicectomy or have had a gynaecological operation. Characteristically the same symptoms have continued since the operation.

Diagnosis. Although the diagnosis is usually suggested by the history alone, organic bowel disease has to be excluded, especially in patients developing symptoms for the first time over the age of 40 years. Rectal examination is normal and the rectum is usually empty. Sigmoidoscopy is essential to exclude an organic lesion of the distal colon. The mucosa appears normal in the irritable bowel syndrome but the colon may show marked motor activity, contracting and relaxing quite unlike the normal inert bowel. Barium enema examination is necessary principally to exclude organic disease; there are no diagnostic radiological features. There is no anaemia and ESR is normal. In patients whose principal complaint is painless diarrhoea, the possibility of lactose intolerance (p. 494) or mild thyrotoxicosis (p. 631) should not be overlooked.

Treatment. Although there is no specific treatment for this disorder, considerable alleviation of symptoms may be achieved by appropriate management of the patient. There is no doubt that nervous tension and anxiety may precipitate or aggravate the condition and there is sometimes an underlying fear of cancer. A negative investigation is important to reassure the patient. A sympathetic approach to the patient combined with a simple explanation of the physiological basis for the symptoms often leads at least to a temporary improvement; if anxiety is a prominent feature, drugs such as diazepam or chlordiazepozide may be necessary. In patients with persistent or troublesome symptoms, other measures designed to modify the intestinal dysmotility are required. For constipation and pain, one of the hydrophilic colloids, e.g. Isogel, should be prescribed in a dose sufficient to ensure a normal bowel movement and the patient should be encouraged to increase the roughage content of the diet. It is important that the patient should stop laxatives. Pain may be relieved by an anticholinergic drug such as dicyclomine three or four times a day. As an alternative meberverine hydrochloride which has a direct effect on smooth muscle, causing it to relax may be prescribed in a dose of 100 mg four times a day. For patients with painless diarrhoea, improvement is commonly obtained with some dietary restriction, particularly the avoidance of fresh fruits and salads. Diarrhoea is treated with an anticholinergic four times a day with a larger dose first thing in the morning since symptoms are often worse at this time. Codeine phosphate and diphenoxylate are useful drugs which act quickly and can be carried by the patient to use in an emergency or they can be taken before any event which is known to precipitate an attack of diarrhoea.

PREVENTION OF DISEASES OF THE DIGESTIVE SYSTEM

Diseases of the digestive system form a large part of the work of hospitals and general practitioners and are of considerable social and economic importance. Many of these diseases affect the young and working sections of the population and many are responsible for recurrent or prolonged ill-health. For example, peptic ulcer both in its acute and chronic forms is a significant cause of disability and work loss. Its liability to chronicity is shared with such conditions as Crohn's disease, pancreatitis and ulcerative colitis. Chronicity and recurrence are themselves indices of failure to cure and are powerful arguments in favour of prevention.

Since little is known of the exact cause of many of the diseases of the digestive system, their prevention is difficult, but nevertheless there is a growing appreciation of the importance of stress, of diet, and of the abuse of alcohol and tobacco, if not in the aetiology, at least in the aggravation of many alimentary disorders. Thus if alimentary disease cannot be prevented, at least its severity can be diminished and its tendency to recur or become chronic can be reduced. Aspects of importance to be considered include:

1. **Control of Infection.** The virtual disappearance of tuberculosis in Britain as a cause of alimentary disease illustrates the value of prevention coupled with effective treatment. Other infections of the alimentary tract continue in the form of food poisoning and dysenteries. Their control awaits improvement in the standards of hygiene in the preparation and handling of food.

2. **Change in Dietetic Habits.** It is increasingly evident that the low residue, highly refined diet of the Western Hemisphere is responsible for disorders of intestinal motility and particularly for diverticular disease and possibly appendicitis. Previously the prerogative of food faddists and cranks, the high bulk, vegetarian type has come to be recognised as important in the treatment, if not prevention, of colonic motility disorders. There are suggestions, too, that food additives to improve flavour and colour and synthetic foodstuffs may be of aetiological significance in carcinoma of the stomach and in Crohn's disease. It follows, therefore, that diet should be as mixed, natural and as high in roughage as possible. It should contain fruit, vegetables and natural cereal in preference to starches, sugars and highly refined flour.

3. **Restriction of Alcohol Intake.** Alcohol, apart from its role in the production of hepatic cirrhosis, contributes to the incidence of chronic pancreatitis and particularly to that of its relapsing form. Alcohol consumption, whether in the form of wine or spirits, should therefore be moderate and should be avoided completely and preferably permanently after pancreatitis and hepatic disease.

4. **Reduction of Tobacco Consumption.** Nicotine delays the healing of gastric ulcer and may play a part in the production of duodenal ulcer. The rate and

permanence of healing of ulcer, and indeed its prevention, can be fostered by the cessation of cigarette smoking.

5. **Elimination of Nervous Stress.** Some disorders of the alimentary system are due to psychological factors while many others, because of their chronicity, have an associated anxiety component. In the latter, cure and the prevention of chronicity and relapse require attention to both physical and psychiatric components.

The avoidance of stress in the prevention of disease is less easy to achieve unless it is possible to identify groups at risk. There is, however, a growing realisation of the need to improve conditions of work, and to take particular care of personnel employed in stressful occupations such as city bus driving and repetitive work such as in mass production assembly lines.

6. **Identification and Surveillance of Pre-cancerous Conditions.** Multiple polyposis and colonic polyps are examples of conditions whose adequate treatment will prevent the development of malignant disease. The high risk of carcinoma in ulcerative procto-colitis, of the development of lymphoma in enteropathies, has led to long-term follow-up to allow prevention and early detection. In countries such as Japan where carcinoma of the stomach is common, population screening by endoscopy allows diagnosis of carcinoma at an early and curable stage.

G. P. CREAN.
D. J. C. SHEARMAN.
W. P. SMALL.

Further reading:

Avery Jones, Sir Francis, Gummer, J. W. P. & Lennard-Jones, J. E. (1968). *Clinical Gastroenterology*, 2nd ed. Oxford: Blackwell.

Cope, Sir Zachary (1968). *The Early Diagnosis of the Acute Abdomen*, 13th ed. London: Oxford University Press.

French, E. B. (1973). Examination of the Alimentary System. In *Clinical Examination*, 3rd ed., edited by Macleod, J. Edinburgh and London: Churchill Livingstone.

Howat, H. T. (1972). *Clinics in Gastroenterology*, Vol. 1, No. 1. *The Exocrine Pancreas*. London: W. B. Saunders.

Spiro, H. M. (1970). *Clinical Gastroenterology*, 1st ed. London: Macmillan.

Diseases of the Liver and Biliary Tract

DISEASES OF THE LIVER

Anatomical Considerations

On histological examination the liver appears to be composed of radial columns of cells arranged in lobules around a central efferent vein. At the periphery of the lobules lie portal tracts, each containing a small branch of the hepatic artery and of the portal vein and a small bile duct. Between the columns of liver cells are sinusoids lined with cells of the reticulo-endothelial system known as Kupffer cells. Small bile canaliculi lie between the liver cells, forming a network which opens eventually into the interlobular ducts situated in the portal tracts.

From the portal vein and from the hepatic artery in the portal tract, blood passes into the sinusoids and reaches the central vein, which drains into the hepatic veins. Mixing of portal venous and hepatic arterial blood appears to occur in the sinusoids. When the normal architecture of the liver, including pre-sinusoidal sphincters on the arterioles, is damaged by disease, direct transmission of the high arterial pressure to the portal system may be partly responsible for the portal venous hypertension found in such conditions.

Bile, secreted by the liver cells, passes, in reverse direction to the blood flow, through canaliculi to the periphery of the lobule. There, the bile ducts are lined with cuboidal epithelium and gradually become larger as they progress to the porta hepatis. Ultimately the common hepatic duct is formed by the union of the ducts from the right and left lobes of the liver, and this, with the cystic duct from the gall-bladder, forms the common bile duct. This usually traverses the substance of the head of the pancreas, where it is joined, in the majority of cases, by the pancreatic duct. The united ducts then open into the second part of the duodenum through the ampulla of Vater, the opening being controlled by the sphincter of Oddi.

Blood Supply. The liver is unique in that the greater part of the blood flowing to it is venous and comes via the portal vein which drains the large and small intestine, stomach, pancreas and spleen. The total blood flow through the adult human liver averages 1,500 ml/minute. This frequently becomes considerably reduced in chronic hepatic disease. Though the hepatic artery supplies only about 20 per cent of the blood to the liver, it carries up to 50 per cent of the oxygen utilised by the organ. The large supply of venous blood results in an oxygen supply that is probably always precarious, so that the liver is vulnerable to chronic hypoxia. In chronic passive congestion, for example, there is degeneration and sometimes necrosis of the cells furthest from the entry of well-aerated blood, i.e. in the centre of the lobule. Centrilobular necrosis is found also in thyrotoxicosis, in which the oxygen demand by the liver cells is increased. In addition, in the majority of acute toxic or infective liver diseases, in which there is neither hypoxia nor excessive oxygen utilisation, necrosis in this zone is commonly found. Damage to the parenchymal cells in these conditions may be aggravated by the relative oxygen deficiency in the centre of the lobule.

The blood supply to the liver through the portal vein is believed to follow two main streams, one from the stomach, spleen and descending colon to the left lobe, and one from the small intestine and ascending colon to the right lobe. This distribution of blood does not correspond strictly to the anatomical lobes of the liver. Acute massive necrosis, which may in part, at least, be due to dietary inadequacy (p. 555), may show damage predominantly in the left lobe, presumably because essential dietary constituents are especially deficient in blood draining the stomach, spleen, and descending colon. Likewise, abscesses from an infected appendix occur mainly in the right lobe.

Metabolic Activities of the Liver

The manner in which blood gains intimate contact with hepatic cells facilitates the rapid transfer of metabolites. Apart from the Kupffer cells of the reticulo-endothelial system, all the cells of the liver are undifferentiated and appear capable of performing the many functions of the liver.

(1) **Carbohydrate Metabolism.** The liver is the most important organ in the body for the maintenance of a normal concentration of blood glucose. It is able to convert glucose, fructose, galactose, glycerol, certain amino acid residues, and 2- and 3-carbon compounds (e.g. lactate, pyruvate and oxalo-acetate) to glycogen. In hypoglycaemia it hydrolyses stored glycogen to glucose. These mechanisms are intrinsic functions of the organ but they are influenced by many extrahepatic factors, e.g. insulin, adrenaline, thyroxine, cortisol and glucagon.

(2) **Protein Metabolism.** The liver is the most important site of deamination of amino acids, as a preliminary step in their interconversion and oxidation. Urea synthesis from the amino groups made available by this process occurs solely in the organ. Plasma albumin, prothrombin, fibrinogen and the other clotting factors, V, VII, IX and X are synthesised perhaps exclusively in the parenchymal cells of the liver. α and β globulins are mainly formed in the liver, while γ globulin is formed by cells of the reticulo-endothelial system. As a result of these syntheses, the protein pattern of the plasma is to a large extent determined by liver function.

(3) **Lipid Metabolism.** The liver plays an important part in fat metabolism. Fats are oxidised in the liver as far as the four carbon chain stage (ketone bodies). The amount of this oxidation depends, *inter alia*, upon the availability of carbohydrate and is greatly increased when sugar is absent as in fasting or when there is difficulty in its use as in diabetes mellitus. The ketone bodies themselves do not appear to be oxidised in the liver and are liberated into the blood stream for peripheral oxidation. Triglycerides are formed in the liver and synthesis of phospholipid from fatty acid, glycerol, phosphate and a nitrogenous base, e.g. choline, also occurs largely in the liver. Cholesterol is synthesised in the

liver and is also esterified there. Cholesterol and triglycerides circulate in the blood as lipoproteins; not only is the liver an important source of these complexes which maintain lipid in colloidal solution, but also it contains an enzyme which can break the lipid-protein bond. Bile salts, the breakdown products of cholesterol, are synthesised in the liver cells and in turn facilitate the excretion of cholesterol in the bile.

(4) **Vitamin Metabolism.** The liver is directly or indirectly concerned with the metabolism of many vitamins. Fat-soluble vitamins depend to some extent for their absorption upon a normal biliary secretion. Vitamins A, D, K, B_{12} and folate particularly are all stored in the liver. Vitamin K is required by the hepatic cells for the production of prothrombin and factor VII. The liver contains enzymes which can convert tryptophane to nicotinic acid and synthesise many coenzymes and prosthetic groups. The phosphorylation of thiamin, which is a necessary preliminary to its function as a coenzyme, the methylation of nicotinic acid and the 25-hydroxylation of vitamin D (p. 136) also occur in the liver.

(5) **Inactivation of Hormones.** Oestrogens, corticosteroids and other steroid hormones are conjugated in the liver with glucuronic acid and excreted in the urine, though other modes of inactivation also occur. Thyroxine and vasopressin are probably inactivated in the liver, but the mechanisms are unknown.

(6) **Detoxication of Drugs.** The liver plays a vital role in the detoxication of drugs as well as endogenous hormones. This is achieved by enzyme systems of broad specificity located on the endoplasmic reticulum (microsomal enzymes). At these sites the drugs are rendered more water soluble and can then be excreted in the bile and urine. Alkaloids such as morphine or atropine are partly destroyed in the liver, ammonia is converted to urea, barbiturates undergo oxidation of their side chain and are rendered pharmacologically inert. Conjugation with glucuronic acid occurs with salicylates, morphine and chloral hydrate, and these conjugates are less active than their precursors. Acetylation of sulphonamides also occurs, though this process makes these drugs less soluble and potentially more harmful.

The duration and intensity of action of many drugs are largely determined by the speed at which they are metabolised by these microsomal enzymes of the liver. The activity of the enzymes can be altered by dietary and nutritional factors or alterations in hormonal balance. The activities of the enzymes may also be markedly increased by the coincident administration of drugs. This increase in activity appears to represent an increased concentration of enzyme protein; it is referred to as *enzyme induction* and may be of great significance in man because of the consequent alteration in duration and intensity of drug action. This enzyme induction may have important therapeutic implications, e.g. a decreased response to coumarin anticoagulants whilst taking barbiturates followed by a markedly diminished dose requirement on withdrawal of the barbiturate. Furthermore, some drugs can stimulate their own metabolism, an effect which may explain the increased tolerance for alcohol of the alcoholic.

(7) **Biliary Excretion.** Bile is produced by the liver and passes through the intrahepatic biliary channels to the common hepatic duct and thence to the gall-bladder. The main constituents, apart from water and inorganic salts, are bilirubin, bile acids, cholesterol, alkaline phosphatase and mucin.

(*a*) *Bilirubin.* Haemoglobin is broken down by reticulo-endothelial cells mainly in the spleen, liver and bone marrow. The bile pigment, bilirubin, is derived from the non-iron-containing residue of haemoglobin after the separation from globin. A small amount of bilirubin is derived from other haem-containing compounds such as haemoglobin precursors in the bone marrow, myoglobin and the cytochromes. In the blood this unconjugated bilirubin (prehepatic bilirubin) is bound to plasma albumin and, as a consequence, does not pass readily through the glomerulus of the kidney into the urine. Unconjugated bilirubin is actively transported from the blood to the bile by the liver cells and during its passage it is separated from its protein and is conjugated with glucuronic acid. Conjugation occurs in the microsomes of the liver cells by the activity of glucuronyl transferase and renders the pigment water-soluble so that it becomes capable of being more freely excreted in the urine. This compound is called conjugated bilirubin. In patients with unconjugated hyperbilirubinaemia the level of bilirubin in the plasma can be lowered by the administration of barbiturates which stimulate microsomal enzyme activity.

In the small intestine conjugated bilirubin is metabolised by bacteria to a series of isomers of stercobilinogen which on oxidation form the main faecal pigment stercobilin. The bulk of these pigments is excreted in the stool (250 mg/day) but some is reabsorbed from the gut. Most of this is excreted by the liver cells into the intestine and a small part is excreted in the urine (2-4 mg/day) where it is called urobilinogen. Urobilinogen and its oxidation product urobilin are chemically identical with stercobilinogen and stercobilin, respectively.

(*b*) *Excretion of Bile Acids and Cholesterol.* Bile acids are the breakdown products of cholesterol. They are synthesised in the liver and conjugated with glycine and taurine to form bile salts which are secreted directly into the bile. Here they may form micelles (p. 488) when in sufficient concentration and these micelles, which also contain phospholipid, permit the solubilisation of cholesterol although its biliary concentration far exceeds its aqueous solubility in a simple solution. An alteration of these solutes in bile is now recognised as a major factor in the precipitation of cholesterol and provides the nidus for gall-stone formation.

In the lumen of the proximal small intestine bile salts are essential for the solubilisation of the products of fat digestion. Lack of this detergent property of bile explains the steatorrhea which, although often latent, is a well recognised feature of hepatobiliary disease. In addition to dietary glycerides there can be malabsorption of fat-soluble vitamins leading to a bleeding tendency (vitamin K), osteomalacia (vitamin D) and night blindness (vitamin A). About 90 per cent of the bile salts are reabsorbed from the distal ileum and return to be re-excreted by the liver. This very efficient enterohepatic circulation preserves the small total body pool of bile salts which may recycle two to three times per meal. Only a small amount (300 mg) of bile salts escapes daily into the colon. When there is disease, resection or bypass of the terminal ileum there is an excessive loss of bile salts in the faeces. In the colon the bile salts have a cathartic action due to interference with the resorption of electrolytes and water. In addition to a troublesome diarrhoea there is also steatorrhea since the liver cannot compensate for the increased loss of bile salt and the concentration of bile salts in the duodenum is insufficient to form micelles. In patients with an overgrowth of bacteria in the small bowel (blind loop syndrome, p. 494) there may be malabsorption of various nutrients and steatorrhea is often a feature. The malabsorption of lipid is believed to be the result of bacterial alteration of the bile salt molecule (deconjugation and dehydroxylation) so that the effective concentration of bile salts in the gut lumen is critically reduced. Similar alterations in the structure of bile salts may also occur in patients with cholangitis. Whilst in pruritus there may be elevated levels of bile salts in the skin and plasma a definite relationship between bile salts and pruritus has not yet been established.

(*c*) *Excretion of Enzymes*. The serum alkaline phosphatase is derived mainly from the intrahepatic biliary system and the level tends to rise when there is obstruction to biliary excretion. An isoenzyme produced by the osteoblasts accounts for a variable proportion of alkaline phosphatase activity in growing children and in diseases of bone. In about 50 per cent of healthy individuals there is in the serum a small amount of alkaline phosphatase which is produced by the intestinal mucosa. Yet another isoenzyme is produced by the placenta and accounts for some of the serum alkaline phosphatase activity in pregnancy. Various malignant tumours, e.g. of lungs and pancreas, have been shown to produce alkaline phosphatase which has similar physico-chemical properties to the placental isoenzyme. The different isoenzymes can be identified by starch gel electrophoresis and studies of enzyme susceptibility to heat inactivation.

Liver Function Tests

Liver function tests are performed for three main reasons:

1. to assist in the differential diagnosis of jaundice (p. 538), with the chief aim of distinguishing between jaundice requiring surgical treatment and jaundice requiring medical treatment;
2. to obtain confirmation of suspected liver disease;
3. to estimate hepatic function as a guide to progress and an aid to prognosis.

The various hepatic functions are not impaired to the same degree in any one case of liver disease, irrespective of its aetiology. As a direct consequence of this differential depression of function, a series of tests covering different functions is best applied. As a corollary, a single negative result of a test indicates neither that the liver is normal nor, if the liver is known to be diseased, that the test is necessarily insensitive.

Extrahepatic obstructive jaundice is not associated with marked parenchymal lesions in the liver, at least in the initial stages. As a result, metabolic functions carried out by the parenchymal cells are not affected, while those activities which involve biliary excretion are impaired. To some extent the reverse situation obtains in hepatocellular jaundice, which usually results from parenchymal damage. Thus the tests of metabolic functions are impaired, and the tests of excretory functions are depressed only in so far as they are a part of hepatic cell metabolism.

TESTS OF METABOLIC FUNCTIONS

The particular functions assessed by these tests are not directly dependent upon the patency of the bile ducts and are therefore normal in the early stages of biliary obstruction. Prolonged biliary obstruction eventually causes parenchymal cell damage, and such functions become impaired in time as a consequence.

Protein Metabolism. The power to synthesise plasma proteins, particularly albumin, is evaluated by determination of plasma albumin and globulin concentrations. In diffuse parenchymal liver disease albumin concentration falls, while there is a rise, for reasons unknown, in the globulin fractions. A quantitative change in the fractions of plasma globulin also occurs, affecting mainly α or γ globulin fractions, particularly the latter, and this may be demonstrated by paper electrophoresis or immunophoresis of the serum. These distortions, with the lowered plasma albumin, provide the physico-chemical basis of *flocculation tests*, which include cephalin-cholesterol flocculation, zinc sulphate turbidity and thymol turbidity and flocculation. These tests are influenced to a varying extent by the different plasma protein components. Since many disorders disturb the plasma protein pattern, e.g. multiple myeloma, the flocculation tests are not specific for liver disease and must always be interpreted in relation to the clinical picture and other laboratory findings. In the early stages of the large majority of cases of jaundice due to extrahepatic obstruction, the flocculation tests are negative or only slightly positive. Because the flocculation tests only reflect the plasma protein pattern many laboratories are discontinuing their routine use for diagnostic purposes in favour of protein electrophoresis.

The distortion of the plasma protein pattern, particularly a fall in fibrinogen concentration, is also responsible for the fact that a low erythrocyte sedimentation rate is sometimes found in the presence of active liver disease.

TESTS WHICH, THOUGH PRIMARILY OF METABOLIC FUNCTION, ARE DEPENDENT UPON THE PATENCY OF THE BILE DUCTS

These tests estimate parenchymal cell hepatic functions which are directly dependent upon the patency of the biliary tree. As a result, they detect alterations in function due either to parenchymal cell damage or to obstruction to the bile ducts.

Serum Alkaline Phosphatase Activity. Normal serum values in adults range from 3 to 12 King-Armstrong (KA) units per 100 ml serum, though levels up to 40 KA units and rarely even higher are found in growing children. In acute or chronic parenchymal liver disease a moderate elevation up to 30 KA units can occur, while in obstructive jaundice concentrations between 30 and 100 KA units are found in the great majority of cases. Values above 50 KA units are also found in many cases of diffuse metastases within the liver. It is to be remembered that high concentrations of serum alkaline phosphatase occur also in conditions in which osteoblastic activity is a feature, e.g. rickets, Paget's disease, hyperparathyroidism and metastatic tumours in bone. Multiple myeloma on the other hand, a malignant disease which affects bone extensively, is not associated with much bone repair and seldom shows a raised serum alkaline phosphatase. High concentrations also occur in the late stages of pregnancy.

Bromsulphthalein Excretion (BSP). This dye, after intravenous injection, is removed from the blood by the parenchymal cells and the Kupffer cells of the liver and excreted in the bile. This capacity may be estimated by determining the concentration of BSP in the blood 45 minutes after the injection when less than 5 per cent of the administered dose is found in the blood of healthy individuals. The normal removal of BSP depends on an intact hepatic blood supply as well as on hepatocyte function. The test is sensitive and is positive in about 80 per cent of cases of infective hepatitis in the pre-icteric phase, and in a very large number of patients with chronic liver disease without jaundice. The test is not useful in the presence of jaundice, by virtue of difficulty in estimation of the dye in the blood in the presence of increased amounts of bilirubin, and because the presence of non-haemolytic jaundice invariably implies hepatic dysfunction.

TESTS OF BILIARY EXCRETION

These tests, though affected to some extent by parenchymal cell damage, are directly dependent upon the patency of the biliary channels. They are used primarily, therefore, in deciding questions regarding the patency of the biliary tree and in estimations of variations in the degree of obstruction present.

Total Plasma Bilirubin. The plasma bilirubin normally ranges from 0·2 to 0·8 mg/100 ml plasma. It is elevated in all forms of jaundice and provides an accurate measure of the depth of the jaundice, and a useful indication of the trend of the disease. Values above 2·0 mg/100 ml coincide with detectable jaundice.

In the majority of parenchymal liver diseases the plasma bilirubin rises to a maximum then gradually subsides as the disease process recedes. Fixed high levels of plasma bilirubin in combination with acholic stools imply complete biliary obstruction, and this occurs most commonly in malignant obstruction of the bile ducts. Fluctuating levels are found in jaundice due to obstruction by gall-stones.

Methods of estimating conjugated and unconjugated bilirubin separately are too complex for routine use. In practice their chemical distinction is of clinical value only in jaundice of the newborn in which the level of unconjugated bilirubin is the important factor in deciding on the need for exchange blood transfusion and in the differential diagnosis of the rare congenital non-haemolytic hyperbilirubinaemias (p. 541).

Urinary Bilirubin. In recent years a test has been devised using a tablet containing a stable diazo dye (Ictotest). This test for bile in the urine is simple, sensitive and inexpensive. If present, then hepatobiliary disease is confirmed;

if absent in a jaundiced patient, then haemolytic disease or a congenital hyperbilirubinaemia is suggested. Bilirubin is present in the urine in cases of obstructive and hepatocellular jaundice, though in the latter it tends to vary inversely with the amount of urobilinogen. It is absent from the urine in haemolytic jaundice.

Urinary Urobilinogen. The simple qualitative test for urobilinogen in urine using Ehrlich's aldehyde reagent may be a helpful procedure in many cases of liver disease and jaundice. The principle of the test is used in an impregnated test-paper strip, Urobilistix. In complete obstructive jaundice bilirubin does not enter the intestine, and therefore urobilinogen disappears from the urine. When there is no obstruction to the biliary channels, an increase in urobilinogen may occur (*a*) because a damaged liver is unable to excrete the normal amounts of urobilinogen presented to it (parenchymal liver disease), or (*b*) because a normal liver is unable to re-excrete adequately the excessive quantity of urobilinogen presented, as occurs in the haemolytic anaemias. Accordingly, in the non-jaundiced patient the presence of an abnormal amount of urobilinogen in a single specimen of freshly voided urine is one of the most sensitive indications of liver damage, provided haemolytic disease can be excluded. It occurs in the congestion of the liver associated with heart failure. Serial tests in typical cases of hepatocellular jaundice reveal the presence of increased amounts of urobilinogen in the early stages, and the absence of bile. As intrahepatic biliary obstruction becomes more severe and jaundice deepens, bilirubin increases in the urine and urobilinogen gradually disappears. Recovery is associated with relief of the obstruction to the canaliculi in the liver so that bile once more enters the intestine. As a result, bilirubin decreases in the urine and urobilinogen reappears.

Tests of Liver Cell Damage

The parenchymal cells of the liver contain certain enzymes in relatively large amounts and these may be released into the plasma when the cell is damaged. Of these the most important for clinical purposes are alanine aminotransferase (glutamic pyruvic transaminase, GPT), and aspartate aminotransferase (glutamic oxalacetic transaminase, GOT), only small amounts of which are present in normal plasma or serum. The source of the enzymes normally present is not known. In patients suffering from acute parenchymal disease of the liver with or without jaundice, the activity of the enzymes rises in the blood above the upper limit of normal (40 units/ml) and usually reaches values of several hundred units within the first few days. In patients with obstructive jaundice the activities of the enzymes are often slightly increased but seldom reach values of over 100 units unless there is co-existing cholangitis. The determinations of serum GPT and GOT are of real value in helping to distinguish hepatocellular jaundice from obstructive jaundice and they are specially helpful in the early diagnosis of infective hepatitis. It should be noted that serum GOT but not serum GPT is elevated in cases of myocardial infarction. Lactate dehydrogenase (LDH) and isocitrate dehydrogenase (ICD) are other enzymes which are released into the plasma when liver cells are damaged. The test most commonly undertaken in Britain is for GPT.

TESTS FOR IMMUNOLOGICAL DISTURBANCE

Considerable evidence is now available of an association between liver disease and disturbances in the normal immune processes. These include the identification of potential antigens, the recognised association of certain liver diseases with other autoimmune disorders and a favourable clinical response in some instances to immunosuppressive therapy.

Hyperglobulinaemia. Raised levels of plasma globulins may be found in all forms of liver disorder, but particularly in chronic liver disease. No specific patterns of disturbance are evident. Immunoglobulins are contained in the β- and γ-regions. IgG increases are most evident in cryptogenic cirrhosis and chronic aggressive hepatitis, IgA levels may be increased in alcoholic liver disease and increased IgM levels are seen most frequently in primary biliary cirrhosis. These changes in the levels of the immunoglobulins are, however, variable and of limited diagnostic significance.

Alpha-fetoprotein. This is an α-globulin normally present in human embryo plasma; it disappears within a few weeks of birth. Its detection in the adult suggests a hepatoma or an embryonal tumour of the testis. The protein is elaborated and detectable in 30-70 per cent patients with hepatoma, the highest rate being found in Afro-Asians.

Autoantibodies. Non-organ specific autoantibodies are not thought to be directly responsible for the progression of hepatocyte or bile canaliculus destruction. Their detection may be of some diagnostic value. They include antinuclear antibody, smooth muscle and antimitochondrial antibodies and are found in the highest titres in three chronic liver diseases, chronic aggressive hepatitis, cryptogenic cirrhosis and primary biliary cirrhosis. The detection of antinuclear antibody may help to identify chronic aggressive hepatitis, but it is also found in a few normal people and in connective tissue and autoimmune diseases which do not involve the liver. Smooth muscle antibody may be found in all three forms of chronic liver disease and is not specific for chronic aggressive hepatitis as was originally believed. Antimitochondrial antibody is a reliable marker of primary biliary cirrhosis where it is positive in at least 85 per cent of patients, whereas it is rarely positive in patients with other forms of obstructive jaundice.

Australia Antigen (*hepatitis associated antigen, HAA*). This was first detected in the serum of an Australian aborigine, hence its name. It has subsequently become recognised that this antigen is closely associated with serum hepatitis. Serum containing the antigen is highly infectious and the antigen may be the coat of the virus particle. It is usually detected by a precipitin reaction and a complement fixation test with specific human antiserum; very sensitive radioimmunoassay methods are also available. The antigen is detectable in about 85 per cent of patients with serum hepatitis within two weeks of the onset of symptoms, although it may be present only for a day or two. Positive antigen status normally persists for three to four weeks. It is an extremely useful marker of infection with type B virus. In a few patients, usually those with depressed immunological responses, the antigen may persist indefinitely although this does not always imply persistent liver disease. Nevertheless this antigenaemia creates problems on account of the risk of transmission of hepatitis by such individuals who cannot be blood donors and who will require special facilities and precautions when submitted to blood-letting procedures. About 0·1 per cent of apparently healthy European and North American people are HAA positive. The antigen has also been found in blood of about 25 per cent patients with apparent acute infective hepatitis and in a similar proportion of patients with chronic aggressive hepatitis. In the former group the infection may have been a faeco-oral transmission of the type B virus. At present no marker for type A virus infection has been identified.

Miscellaneous Procedures

Liver Biopsy. Biopsy may give clear evidence of viral hepatitis, drug induced hepatitis, cholestatic hepatitis, primary biliary cirrhosis, chronic liver disease, extrahepatic obstruction or hepatic malignant disease. It is a simple procedure in the hands of an experienced clinician. Using a local anaesthetic the liver is entered percutaneously through an intercostal space. If there is massive hepatomegaly a subcostal approach may be preferred. The procedure requires the active co-operation of the patient since respiration must be arrested at the moment of hepatic puncture. The risk of haemorrhage demands a normal coagulation mechanism. A prolonged prothrombin time may be corrected by the administration of vitamin K_1. In some centres a plasma concentrate rich in prothrombin and Factors VII, IX and X is available. A further problem is that in patients with extrahepatic obstruction there is an increased risk of bile leakage and peritonitis.

Peritoneoscopy. This may also be of value in the investigation of hepatobiliary disease. This procedure involves the creation of a tense pneumoperitoneum which permits the inspection of the peritoneal surfaces of the liver and gallbladder. A liver biopsy may also be obtained under direct vision. The procedure is not possible in the presence of adhesions and requires the use of an operating theatre. It is associated with more risk to the patient than hepatic biopsy.

Radioisotope Studies. Two types of study are available. Radioactively labelled sulphur colloid is concentrated in the reticulo-endothelial system and so provides an anatomical study of the organ. Labelled Rose Bengal, however, is actively excreted by the hepatocytes and provides both an anatomical and functional study. Scanning is useful in delineating tumours, cysts or abscesses of the liver.

JAUNDICE

Jaundice or icterus is a condition characterised by increase in the bilirubin of the blood above the normal range of 0·2-0·8 mg/100 ml plasma. When the increase is slight (plasma bilirubin <2 mg/100 ml) its presence can often be detected only by plasma analysis, and latent jaundice is then said to exist. When the increase is greater, there is visible yellow colouration of the skin, sclerae and mucous membranes, and clinical jaundice is present. Internal tissues are also stained. Bilirubin does not pass the blood-brain barrier except in the immediate neonatal period. Pathological mechanisms giving rise to jaundice fall into three groups: haemolytic, hepatocellular and obstructive (Fig. 74).

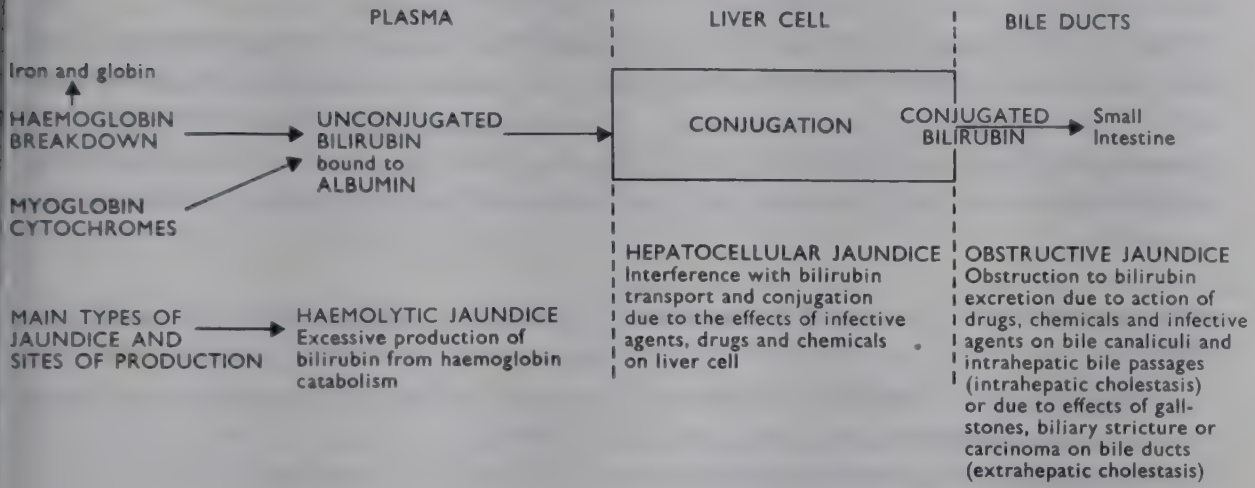

PLASMA
LIVER CELL
BILE DUCTS
Iron and globin
HAEMOGLOBIN BREAKDOWN
UNCONJUGATED BILIRUBIN bound to ALBUMIN
CONJUGATION
CONJUGATED BILIRUBIN
Small Intestine
MYOGLOBIN CYTOCHROMES
HEPATOCELLULAR JAUNDICE
Interference with bilirubin transport and conjugation due to the effects of infective agents, drugs and chemicals on liver cell
OBSTRUCTIVE JAUNDICE
Obstruction to bilirubin excretion due to action of drugs, chemicals and infective agents on bile canaliculi and intrahepatic bile passages (intrahepatic cholestasis) or due to effects of gall-stones, biliary stricture or carcinoma on bile ducts (extrahepatic cholestasis)
MAIN TYPES OF JAUNDICE AND SITES OF PRODUCTION
HAEMOLYTIC JAUNDICE
Excessive production of bilirubin from haemoglobin catabolism

FIG. 74

Bilirubin excretion pathway and main types of jaundice.

1. **Haemolytic Jaundice** (p. 735)

Excessive destruction of red blood cells results in increased bilirubin formation. The liver excretes conjugated bilirubin into the intestine to the maximum of its capacity, and a healthy liver can handle a bilirubin load about six times greater than normal before unconjugated bilirubin accumulates in the plasma. This accounts for the fact that, except in the newborn when the bilirubin conjugating mechanism is immature, jaundice due to haemolysis is usually mild.

Causes. The rate of destruction of red blood cells is increased either because of a congenital defect in the red cells which renders them unduly fragile (congenital spherocytosis, sickle cell anaemia, thalassaemia) or because various extra-corpuscular factors act on the red cells and cause excessive haemolysis. These factors include infections, poisons and circulating red-cell antibodies as in autoimmune acquired haemolytic anaemia, incompatible blood transfusion and haemolytic disease of the newborn.

Clinical Features. The following features are common to all types of haemolytic jaundice and are independent of its cause. The jaundice may be latent or overt but is rarely severe, the total plasma bilirubin being less than 4 mg/100 ml. Enlargement of the spleen is found in the majority of the cases and is due to excessive activity of the reticulo-endothelial system. Reticulocytosis is almost invariably present, but the degree of anaemia varies with the severity of the haemolytic process and the power of the bone marrow to increase its productive activity. The stools are brown or orange in colour and contain large amounts of stercobilinogen and stercobilin. Part of the stercobilinogen in the intestine is reabsorbed and appears in the urine (urobilinogen). Freshly voided urine is therefore of normal colour, since no bilirubin is present, but oxidation of excess urobilinogen to urobilin quickly renders the urine dark. Tests of liver function which are dependent upon parenchymal cell metabolic activities are normal.

2. Hepatocellular Jaundice

This type of jaundice is usually associated with damage to the parenchymal cells of the liver by toxic or infective agents, the power to transfer bilirubin from the blood to the biliary canaliculi being, in consequence, diminished. The cellular degeneration and necrosis permit diffusion into the blood of bilirubin that has reached the canaliculi; swelling of the cells and oedema cause intrahepatic cholestasis.

Causes

1. The viruses of infective and serum hepatitis are by far the most important cause of hepatocellular jaundice (p. 545).
2. Other infections include leptospirosis, yellow fever and septicaemia.
3. Toxic substances (p. 544).
4. Deficiencies of specific food factors, e.g. cystine, tocopherol and selenium produce liver damage in experimental animals. The extent to which this observation is relevant to acute massive necrosis and hepatic infiltration with fat in man is not known.
5. Immaturity of the enzyme mechanisms responsible for the conjugation of bilirubin. This occurs in the newborn and is more pronounced in the premature infant.
6. Congenital defects in the mechanisms for transport and conjugation of bilirubin (p. 541).

Clinical Features. The clinical features of hepatocellular jaundice vary according to the aetiology. Icterus may be mild or very severe. For further details of the clinical picture and laboratory data of a typical example of hepatocellular disease see pages 546 to 547.

3. Obstructive Jaundice

Obstructive jaundice occurs when there is a block to the pathway between the site of conjugation of bile in the liver cells and the entry of bilirubin into the duodenum. Stasis occurs within the bile ducts and the canaliculi, and conjugated bilirubin and other constituents of bile are retained; these then enter the blood stream.

Causes. Obstructive jaundice may be broadly divided into two categories: (*a*) extrahepatic cholestasis where there is obstruction to the main bile ducts, and (*b*) intrahepatic cholestasis where the lesions responsible lie within the liver between the cells and the main bile ducts.

(*a*) *Extrahepatic Cholestasis.* The most common causes are impaction of gallstones in the common bile duct and carcinoma of the head of the pancreas or rarely of the ampulla of Vater. Other causes include stricture of the bile duct, inflammation and scarring around a duodenal ulcer and metastatic carcinoma of lymph nodes in the porta hepatis.

(*b*) *Intrahepatic Cholestasis.* This occurs in the presence of patent main bile ducts and is of multiple aetiology. Certain drugs commonly employed in clinical practice occasionally produce jaundice of this type. With some drugs the effect is a sensitivity reaction while with others the evidence points to direct toxicity (p. 544); the jaundice is caused by stasis from inflammation and oedema in the intrahepatic biliary canaliculi.

Intrinsic disease of the liver itself is often associated with intrahepatic cholestasis, and complicates the jaundice which occurs in diseases which damage hepatic cells, e.g. infective hepatitis.

Clinical Features. Apart from the features of the causative disease, these include yellow colouration of sclerae and skin, pale or clay-coloured bulky stools containing an excessive amount of fat and a deficiency of stercobilinogen, and dark urine due to the presence of bilirubin. Pruritus, anorexia and a metallic taste in the mouth may occur. Owing to the impairment in fat absorption in the intestine as a result of the absence of bile salts, vitamin K absorption is diminished, with consequent increase in coagulation time and in the one-stage prothrombin time from prothrombin and factor VII deficiency, and a tendency to haemorrhage. Tests of liver function which are dependent upon the metabolic activities or integrity of the parenchymal cells, e.g. flocculation tests, tend to be normal in the initial stages. There is usually, however, slight elevation of the serum enzyme levels (p. 536). More definite elevation of serum enzyme levels is seen in patients with cholangitis and in such patients it may prove difficult to distinguish between hepatocellular disease and predominantly obstructive disease on the basis of liver function studies alone. In long-standing obstructive jaundice, parenchymal liver cell damage occurs, with consequent impairment of metabolic function, and ultimately a drowsy, semi-stuporous state may ensue (hepatic encephalopathy).

Congenital Non-haemolytic Hyperbilirubinaemias

Congenital disturbances of bilirubin transport and conjugation are rare and are known as the congenital non-haemolytic hyperbilirubinaemias. They have to be considered in differential diagnosis when a patient's jaundice cannot be explained on the basis of haemolytic disease, hepatocellular damage or biliary obstruction. The main disorders are Gilbert's syndrome, Crigler-Najjar syndrome and Dubin-Johnson syndrome (Fig. 75).

Gilbert's syndrome. This usually presents in adolescents or young adults and may be inherited as an autosomal dominant with impaired penetrance. It often comes to light after an attack of viral hepatitis, the patient making a complete clinical and biochemical recovery except that mild icterus persists. The patient suffers variable and slight jaundice due to unconjugated hyperbilirubinaemia which is not caused by significant haemolysis. There may be occasional anorexia, nausea and upper abdominal pain when jaundice deepens, often in relation to infection or fatigue. The defect is believed to lie either in the transport of unconjugated bilirubin from the plasma into the liver cell or in conjugation. Apart from a raised plasma bilirubin level which is usually less than 6 mg/100 ml, the liver function tests are normal and the liver is also normal histologically.

Crigler-Najjar syndrome. This very rare condition is inherited as an autosomal recessive. It is due to deficiency of the conjugating enzyme in the liver cell, glucuronyl transferase. In its severest form it gives rise to marked unconjugated hyperbilirubinaemia which in the newborn leads to kernicterus and early death. Cases in which the enzyme deficiency is mild live to adult life. The jaundice in these patients tends to be more severe than in patients with Gilbert's syndrome but otherwise the two conditions are difficult to distinguish. The liver function tests other than the plasma bilirubin level are normal and liver histology is also normal.

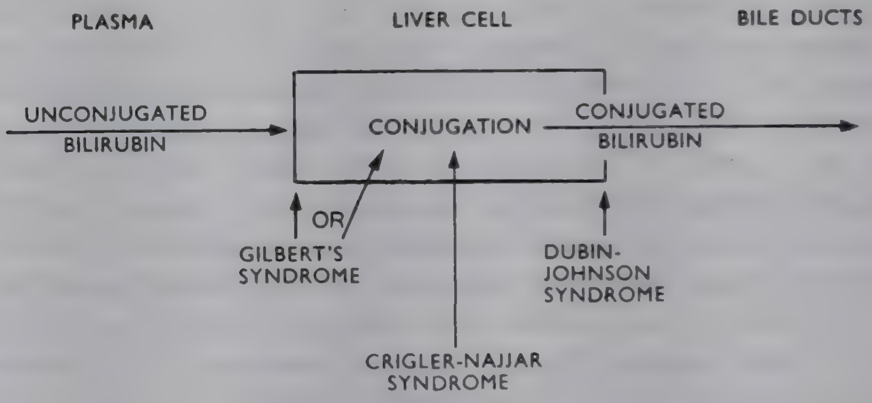


FIG. 75

Site of defect in main varieties of congenital non-haemolytic hyperbilirubinaemias.

Dubin-Johnson syndrome. Like Gilbert's syndrome this tends to occur in young adults and causes variable mild jaundice and vague ill health. It is a conjugated hyperbilirubinaemia inherited as an autosomal recessive characteristic; bilirubin may appear in the urine and the stools may be pale. The defect in this condition is believed to be in the mechanism for transport of conjugated bilirubin from the liver cell into the bile canaliculi. Apart from a raised plasma bilirubin level, which is usually less than 6 mg/100 ml and mostly due to conjugated bilirubin, the routine liver function tests are normal. The BSP excretion test (p. 535) shows normal or nearly normal clearance from the plasma after 45 minutes but then later samples taken at 90 minutes and 120 minutes show a rise of BSP in the plasma due to BSP conjugates which are slowly cleared from the blood in the next several hours. Liver biopsy shows dark pigmentation of liver cells, mainly in the centrilobular region due to the deposition of a pigment believed to be melanin. Bilirubin, BSP and cholecystographic media probably share excretory pathways in the liver. This may account for the abnormal BSP clearance in the Dubin-Johnson syndrome and also for the fact that many patients show poor visualisation of the gall-bladder after oral cholecystography.

A very similar condition without the liver pigmentation has been described from the Philippines. It is known as the *Rotor syndrome*.

It has to be stressed that the prognosis is excellent in these patients. Apart from the congenital defect in the metabolism of bilirubin, liver function and structure are completely normal. The patient should be advised accordingly.

Effect of Drugs on Bilirubin Metabolism

Numerous drugs and chemicals affect bilirubin metabolism and knowledge of these actions is essential in the differential diagnosis of jaundice and hepatobiliary disease and in the investigation and management of patients with such disorders. The sites of action of some drugs and chemicals are illustrated in Figure 76.

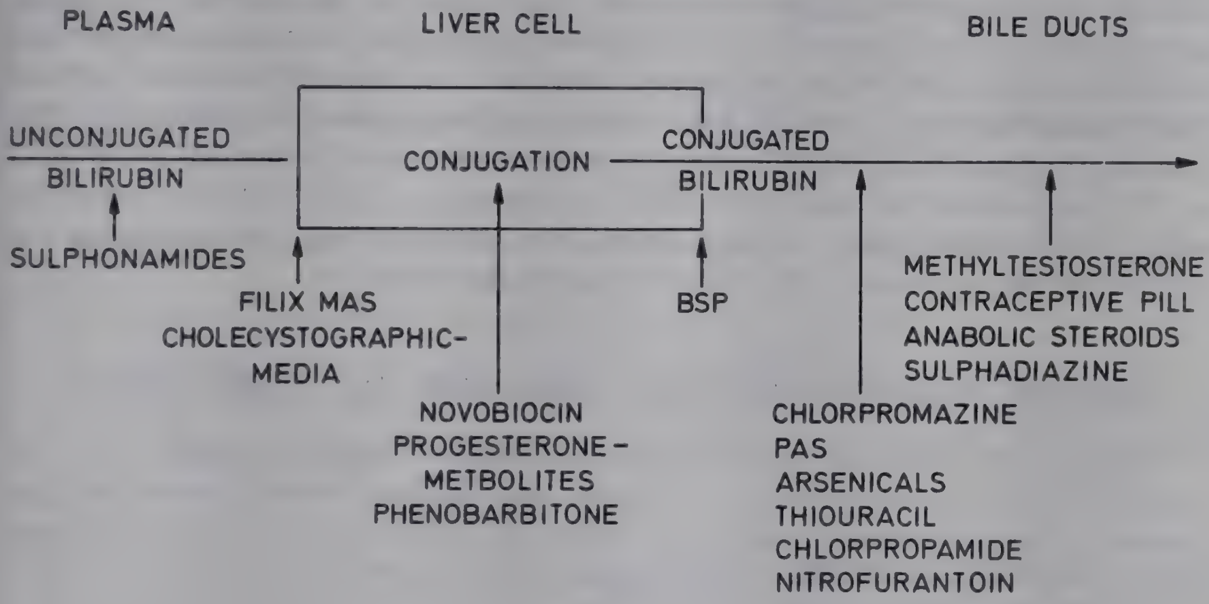


FIG. 76

Sites of action of some drugs that affect bilirubin metabolism.

Sulphonamides compete with bilirubin for binding with albumin. Hence displacement of unconjugated bilirubin from albumin by a sulphonamide could occur in the newborn infant suffering from haemolytic disease and increase the chance of his developing kernicterus. This might arise if the infant were given sulphonamide therapy or, more likely, if the mother received sulphonamides in the late stages of pregnancy.

Filix mas which is used in the treatment of taeniasis (p. 983) sometimes causes mild unconjugated hyperbilirubinaemia. The responsible factor in filix mas is believed to be flavaspidic acid and it gives rise to a defect in transport of unconjugated bilirubin into the liver cell. A similar effect is occasionally seen after the use of cholecystographic media. Novobiocin and certain progesterone metabolites may inhibit the activity of glucuronyl transferase and also cause unconjugated hyperbilirubinaemia.

By contrast phenobarbitone is an example of a drug causing enzyme induction (p. 531); it potentiates the activity of glucuronyl transferase. Phenobarbitone reduces the unconjugated hyperbilirubinaemia in haemolytic disease of the newborn and in Gilbert's syndrome. In epileptics on long-term treatment with phenobarbitone the average total plasma bilirubin level is significantly lower than in the general population.

BSP may cause a transient rise in plasma bilirubin because it apparently interferes with the transport of conjugated bilirubin out of the liver cell into the bile canaliculi. Hence routine liver function tests should be done before and not immediately after the performance of a BSP excretion test.

As already indicated (p. 541) a number of drugs cause an obstructive type of jaundice because they may produce inflammatory changes sometimes with eosinophilia which affect the intrahepatic biliary canaliculi. Not only is the plasma bilirubin raised but the serum alkaline phosphatase is also usually elevated. Some drugs act on the basis of individual hypersensitivity, e.g. chlorpromazine, while others always cause cholestasis if enough is given, e.g. methyl testosterone. Acting like chlorpromazine and other phenothiazine derivatives are para-aminosalicylic acid, arsenical compounds, thiouracil, chlorpropamide and nitrofurantoin. Acting like methyltestosterone are anabolic steroids such as norethandrolone and oxymetholone and the sulphonamide, sulphadiazine. The steroids that have been implicated in causing intrahepatic cholestasis are all C17 α-alkyl substituted testosterones. This is important since oral contraceptives contain such compounds; reactions from their use have been rare in Britain but comparatively common in Scandinavia and South America.

ACUTE PARENCHYMAL DISEASE OF THE LIVER

Parenchymal disease of the liver may be acute, subacute or chronic. In some cases, chronic parenchymal liver disease may be attributable to a previous episode of acute hepatic disease; in others the condition is insidious in onset and no frank history of acute liver disease can be elicited.

Aetiology. Acute parenchymal liver disease is the result of hepatic cell degeneration or necrosis. This is brought about largely by the action of infective or toxic agents. Immunological and nutritional factors may also play a part.

INFECTIONS. Virus of acute infective hepatitis, of serum hepatitis and of yellow fever; leptospirosis; severe septicaemia, e.g. due to *Esch. coli*; severe cases of infectious mononucleosis; infection with *Entamoeba histolytica*.

TOXIC SUBSTANCES. Carbon tetrachloride; ethylene glycol; methyl chloride; phosphorus; chloroform; halothane; dinitrophenol; tetrachlorethane; cinchophen; mepacrine; arsenic and antimony compounds; gold-containing compounds; ferrous salts; poisonous fungi (*Amanita phalloides*) and aflatoxin from *Aspergillus flavus*; sulphonamides; isoniazid; paracetamol; para-aminosalicylic acid; phenylbutazone; thiouracil; mono-amine oxidase inhibitors, phenipraxine, phenelzine and nialamide; acute over-indulgence in alcohol.

Of the above infective and toxic agents, infection with the viruses of infective and serum hepatitis and poisoning with alcohol or carbon tetrachloride are the most common. The implications of halothane have been much debated. It is a most valuable anaesthetic but there is good evidence that on repeated exposure hepatocellular necrosis occurs in rare individuals, probably on a hypersensitivity basis. Hence halothane should be reserved for major operative procedures.

In addition, hepatic cell degeneration and necrosis may accompany hyperemesis gravidarum and eclampsia. The respective parts played by infective, toxic and nutritional factors in the aetiology of these two conditions are not known.

The severity of the illness following hepatic injury from any cause varies with a number of factors which include the nature and virulence of the infecting organism or the size of the dose of the toxic agent, and the resistance of the patient. The last represents the reaction of the patient to hepatic insult and is determined by the existing nutritional state, the occurrence of previous liver damage and the resulting degree of hepatic reserve, individual idiosyncrasy, the age of the patient, heredity and perhaps other factors. In general, the susceptibility of the liver to toxic agents is increased when it is depleted of glycogen as a result of partial starvation. In addition, an adequate supply of protein has been shown to be necessary for the maintenance of the resistance of the liver to injury, and this seems to be related to the intake of the sulphur-containing amino acids, methionine and cystine.

Pathology. The damage to the liver falls into two more or less clearly defined forms:

1. Acute zonal necrosis, in which necrosis occurs in the same zone of all the lobules of the liver, the central zone being most commonly affected.
2. Acute massive necrosis in which widespread necrosis affects entire hepatic lobules throughout large expanses of the liver, sometimes leaving other areas relatively unharmed.

Although these types of necrosis are to some extent determined by the severity of the disease, irrespective of the aetiological agent, certain agents typically tend to produce one or other of the patterns of necrosis. Viral hepatitis is, for example, a common cause of centrilobular necrosis. The other agents which tend to produce zonal necrosis include carbon tetrachloride, phosphorus, chloroform, arsenic and gold, and it occurs in hyperemesis gravidarum and eclampsia; zonal necrosis is also found in some cases of yellow fever and leptospirosis.

Massive necrosis of the liver is associated with a very much more severe clinical picture than is zonal necrosis and may occur as an exaggerated reaction to agents which usually produce zonal necrosis. The relatively high incidence of massive hepatic necrosis in tropical countries with poor standards of nutrition, and during pregnancy and lactation suggests that direct or conditioned deficiency of animal protein or amino acids may be a contributory factor.

The distinction between these types of necrosis, although not always clinically possible, is of importance because of the different clinical and pathological courses which they subsequently follow.

Viral Hepatitis

Two conditions, infective hepatitis and serum hepatitis, are very similar in respect of their clinical and pathological features. The differences are in the principal modes of infection, incubation period and severity. Light has been thrown on the problem by the discovery of the Australia antigen (p. 537).

Acute Infective Hepatitis

(INFECTIOUS, EPIDEMIC, VIRUS TYPE A,
SHORT INCUBATION, MS1 HEPATITIS)

In its clinically recognisable form this common infectious disease is characterised by jaundice, pyrexia, a short incubation period and a low mortality rate. It is due to a virus which may be spread by human faeces and which usually enters the body by the oral route. Occasionally it may enter the body through infected blood as in the case of serum hepatitis.

Infective hepatitis may be contracted by direct personal contact either with cases incubating or suffering from the disease, or with apparently healthy carriers of the virus. In some epidemics, water, milk and shellfish have been incriminated as vehicles of infection. The incubation period is 15 to 50 days. Children are most commonly affected. When there is overcrowding and poor sanitary conditions the disease is frequently epidemic, e.g. in mental institutions or refugee camps.

Pathology. Although the disease is generalised with some involvement of the gastrointestinal tract, heart, pancreas, spleen, etc., the main lesion is in the liver and consists of a zonal necrosis affecting the centrilobular cells; in the typical case the reticulin framework of the liver is not involved and the hepatic architecture is correspondingly not deranged. In the vast majority of cases this permits complete regeneration of liver lobules without distortion or fibrosis when recovery occurs. Swelling of the parenchymal cells, with associated inflammatory cell infiltration, results in compression of the small intrahepatic biliary ducts with dilatation of the intralobular ductules and canaliculi. Intrahepatic obstructive jaundice is thus superimposed upon hepatocellular jaundice. In some cases hepatic cell necrosis may be slight and the main lesion consist of inflammation around the biliary canaliculi, giving rise to intrahepatic cholestasis.

Clinical Features. In the case of average severity, prodromal symptoms precede the development of jaundice by a period of from a few days to two weeks. They are the usual manifestations of an acute infectious disease, and include chills, headache and malaise. Gastrointestinal symptoms may be prominent; anorexia and distaste for cigarettes are common and early complaints, and nausea, vomiting and diarrhoea may follow. A non-colicky upper abdominal pain occurs as a result of stretching of the peritoneum over the liver as the organ enlarges; the pain is severe in some patients. Physical signs are scanty in the initial stages; the liver is usually tender, though not readily palpable. Tender enlarged cervical lymph nodes may be found and splenomegaly may occur, particularly in children.

The appearance of bile in the urine and a yellow tint to the sclerae heralds the onset of jaundice. As the element of obstruction to the biliary canaliculi develops, the jaundice deepens, the stools become paler and the urine darker, while the liver becomes more easily palpable. At this time the appetite often improves and gastrointestinal symptoms diminish in intensity. Thereafter the jaundice usually recedes, the stools and urine regain their normal colour, the liver enlargement regresses and, in the course of three to six weeks the great majority of cases gradually recover. Milder cases occur or the disease may run a non-icteric course which is recognised by the association of vague gastro-intestinal complaints or malaise with biochemical evidence of hepatic dysfunction.

Course and Prognosis. In the vast majority of patients the clinical illness is straightforward but many feel debilitated for two to three months afterwards. In anxious introspective patients too frequent clinical and biochemical evaluation in the convalescent period may lead to the development of the post-hepatitis syndrome of malaise, nausea and right hypochondrial discomfort in the absence of clinical, biochemical or histological evidence of liver disease. A reassuring attitude is therefore to be adopted during convalescence. The mortality in children and young adults is about 0·2 per cent. A small number tend to relapse in late convalescence; this can sometimes be attributed to too early resumption of activity or neglect of advice about abstinence from alcohol. In these cases the symptoms and signs return and subsequently subside completely without therapy (see chronic persistent hepatitis, p. 557).

Occasionally a moderately severe attack of infective hepatitis may not be followed by subsidence of activity and healing of the liver. Serial biopsy studies may show a continuation of focal hepatic cell degeneration and inflammatory cell infiltration, with increasing fibrosis, over many months or years (chronic aggressive hepatitis, p. 557). There may be no symptoms until chronic hepatic insufficiency develops; occasionally recurrent symptoms and signs such as abdominal discomfort, intolerance to fat, bouts of jaundice and diarrhoea, pruritus, and persistent elevation of plasma bilirubin, may continue to the stage at which hepatic cirrhosis is fully established. It is not known whether the development of chronic hepatitis is due to the persistence of the virus infection or the result of an autoimmune mechanism.

Rarely the disease is fulminant and death ensues in the acute phase, often associated with renal failure. Such cases are sometimes those in whom a superimposed nutritional factor increases the susceptibility of the liver cells to necrosis, e.g. as a conditioned deficiency in pregnant women, elderly patients, and alcoholics in Britain, or as a direct deficiency in persons taking a poor diet lacking in animal protein, as occurs commonly in Asia and Africa. The mortality in these groups may be as high as 50 per cent. Clinically, jaundice increases, and the features of acute massive liver necrosis may develop (p. 549). Occasionally, in such cases, the patient survives the acute phase, only to develop at a later date the symptoms and signs of chronic hepatic insufficiency, due to post-necrotic scarring (p. 561). Hormonal imbalance appears to affect the course of the disease and girls at menarche and women at the menopause are apparently more susceptible to hepatitis.

Laboratory Data. The urine contains excess urobilinogen in the initial stages of infective hepatitis before the appearance of visible jaundice. Urobilinogen increases in the urine as jaundice develops. If complete intrahepatic biliary obstruction occurs, urobilinogen temporarily disappears from the urine and bilirubin becomes detectable. A mild degree of proteinuria is usual. Plasma bilirubin is elevated in most cases. Serum flocculation tests (p. 534) are positive in over 90 per cent of cases and are of value in doubtful cases in which differential diagnosis from extrahepatic obstructive jaundice is difficult. Other tests of parenchymal function may show corresponding depression. SGPT is elevated in the early stages of the disease to 100-2,000 units/ml; indeed estimation of SGPT is the best diagnostic test in the pre-icteric phase of the disease and is particularly helpful in screening contacts. Serum alkaline phosphatase is usually less than 30 KA units/100 ml but when cholestatic jaundice is marked it may be considerably elevated. The total white count is either normal or less than normal in the uncomplicated case, and there may be a relative lymphocytosis. This finding is of considerable diagnostic value and helps to distinguish the condition from Weil's disease (p. 552). Examination of the blood for Australia antigen is negative.

Differential Diagnosis is discussed on page 551.

Treatment. There is no specific therapy for acute infective hepatitis. Chemotherapeutic agents and antibiotics have been shown not to be effective. Infectivity is greatest in the early stages of the disease before jaundice has developed. Isolation is unnecessary, but the ordinary precautions for preventing spread of enteric infections should be adopted. For many years patients have been nursed in general medical wards without evidence of cross infection of other patients. Supportive therapy including suitable modifications to the diet, which should be applied to all types of acute parenchymal liver disease is discussed on page 552.

Prevention. The difficulty in diagnosing the sporadic case before the onset of jaundice renders preventive measures virtually impossible. The problem is further aggravated by the doubt which exists with regard to the mode of transmission and the fact that infectivity is greatest during the pre-icteric phase. The value of case reporting as a preventive measure has been grossly neglected. Gammaglobulin is of undoubted value for clinical virus A hepatitis and should be given to those at high risk, e.g. close contacts of patients with infective hepatitis.

Serum Hepatitis

(Post-transfusion, Virus Type B, Long
Incubation, MS2 Hepatitis)

This form of viral hepatitis has been shown to occur in a small proportion of patients after transfusion with blood, serum or, especially, pooled dried human plasma and in those receiving measles, mumps or yellow fever inoculations. It has been noted also after intradermal, subcutaneous, intramuscular or intravenous injections or following venepuncture for the withdrawal of blood. Under these circumstances contamination of syringe or needle with the virus is responsible. This also explains the high incidence among drug addicts. There have been a number of outbreaks in haemodialysis and organ transplant units. Much blood is used in these units and patients with renal failure may be particularly vulnerable. The disease can also spread by the sexual route and the faecal-oral route, e.g. in male homosexuals. The incubation period of serum hepatitis is usually greater than for infective hepatitis but ranges from 15 to 100 days and in occasional patients it is even longer. The role of the hepatitis associated antigen has been discussed on page 537.

Although the majority of the post-transfusion cases of hepatitis belong to an older age-group than patients with infective hepatitis and many have serious underlying illness which made blood transfusion necessary, the virus causing serum hepatitis appears to be much more virulent than that causing infective hepatitis. The mortality in serum hepatitis ranges up to 30 per cent in different series while that of infective hepatitis is much less than 1 per cent.

Treatment. There is no specific treatment for serum hepatitis at the present time. Supportive therapy is described on page 552.

Prevention. In serum hepatitis the value of immunoglobulin is less certain than in infective hepatitis; a specific hyperimmune globulin is currently under assessment. Clearly the ultimate prevention of hepatitis depends upon the isolation and culture of the specific virus in the laboratory and the development of a vaccine.

The occurrence of serum hepatitis can be prevented to a large extent by screening blood donors and eliminating all those giving a history of jaundice. In the future the development of tests for the Australia antigen may prove to be of value in identifying those donors who are particularly likely to transmit hepatitis. The use of liquid plasma, stored for three to six months, appears to result in the smallest incidence of serum hepatitis. The highest incidence (5 to 10 per cent) follows the use of large pools of dried plasma. If, however, pooling of dried plasma cannot be avoided for practical reasons, the pool size should be no greater than 10 donors.

Adequate sterilisation of syringes and needles is essential. Ideally, this is accomplished by autoclaving syringes and needles for 20 minutes at 120° C. Alternatively disposable needles and tubing should be used. In the absence of these facilities, syringes and needles should be washed in 2 per cent lysol, then boiled in water for 20 minutes. These precautions are especially necessary when venepuncture is to be undertaken.

Acute Massive Liver Necrosis

(ACUTE YELLOW ATROPHY)

This rare condition, which is more common in women, is characterised by the acute onset of massive cell necrosis, shrinkage of the liver, deep jaundice, mental confusion, aminoaciduria, coma and usually death. It occurs uncommonly in the course of viral hepatitis and Weil's disease and is seen occasionally in pregnancy complicated by eclampsia. A few cases are due to intoxication with one or other of the agents mentioned on page 544.

Pathology. Histologically, the liver shows extensive parenchymal cell necrosis. Large expanses of liver tissue are affected, leaving other areas relatively unharmed; in the most severe cases, the whole hepatic parenchyma may become necrotic. The organ is enlarged in the initial phase; as the necrotic tissue is absorbed, the organ becomes correspondingly small. If recovery occurs, the normal architecture of the organ is destroyed: massive strands of fibrosis replace dead tissue, and this, with irregular regeneration of liver cells in other areas, eventually leaves the organ shrunken and coarsely nodular (post-necrotic scarring, p. 561).

Clinical Features. General weakness, nausea, vomiting and complete anorexia occur at the outset. Pyrexia invariably develops later, even in the absence of infection. Pain in the right hypochondrium is common. Jaundice, hepatocellular in type, occurs rapidly, becomes very intense, and may fluctuate. The breath often has a characteristic and pungent odour, known as foetor hepaticus. This is probably due to the presence of methyl mercaptan, which has been shown to be excreted in the urine of such subjects. A generalised haemorrhagic tendency is common and is an ominous feature. Petechiae, ecchymoses, haematemesis, melaena and menorrhagia occur as a result of deficiency of coagulation factors and perhaps also abnormal fibrinolysis. On physical examination, the liver is enlarged in the first instance, but subsequent shrinkage of the organ is common and can be noted from day to day. The spleen is usually only slightly enlarged. Generalised oedema and ascites occur in some cases, as a result of a disturbance in water metabolism and of an alteration in plasma protein concentration.

Course and Prognosis. The majority of patients with acute massive necrosis show cerebral manifestations. Changes of mood, inappropriate, often aggressive, behaviour, confusion or drowsiness are usually the earliest detectable signs. Yawning and hiccoughing may be severe. There is evidence of central nervous system involvement, with extensor plantar reflexes, muscle spasticity, choreiform movements and epileptiform convulsions. A flapping tremor of the hands demonstrated by extending the patient's arms is characteristic but not specific to severe hepatic failure. Hyperventilation is common and oliguria and a pronounced rise in temperature occur. Death takes place usually within a week. The mechanism of production of these symptoms and signs is not fully understood. Their very rapid onset and their rapid reversal in the occasional patient responding to successful therapy suggests a metabolic cause rather than brain cell damage. They result from gross hepatic insufficiency and may be due to the entry into the systemic circulation of toxic nitrogenous substances absorbed from the intestine.

Profound hypoglycaemia requiring massive amounts of glucose for correction may occur. Hypokalaemia, hyponatraemia and changes in acid-base balance are common. Renal failure with severe oliguria may be a terminal event. Depression of brain-stem function may lead to failure of respiratory and vasomotor control and these changes may aggravate the hepatic and cerebral dysfunction. Infection, particularly bacteraemia, is an added hazard. An abnormally high concentration of ammonia in the arterial blood and cerebrospinal fluid is usually found but, although the level of arterial ammonia tends to parallel the severity of clinical illness, ammonia is not considered to be the cerebral intoxicant.

A few cases survive the acute attack only to die from further repeated episodes of acute necrosis. Others recover and eventually become symptom-free for a period. A nodular liver, frequently enlarged and palpable from extensive regeneration hyperplasia, remains as evidence of the previous attack. In the end, these patients develop the symptoms and signs of cirrhosis of the liver (p. 558).

Laboratory Data. The severity of the jaundice is reflected in a plasma bilirubin concentration usually higher than in jaundice from any other cause. The tests for hepatocellular damage are positive (pp. 534-535). Cholesterol ester disappears from the blood. The derangement of protein metabolism is so severe that many amino acids accumulate in the blood and can be found in the urine by chromatographic methods. Abnormal amounts of tyrosine and leucine in the urine have been recognised as a feature of severe liver damage for many years; they tend to crystallise in the urine when present in high concentrations and can be recognised on microscopic examination of a centrifuged deposit of urine. The prothrombin time rapidly becomes prolonged, an effect due to reduction in the hepatic synthesis of coagulation factors and to the consumption of clotting factors in disseminated intravascular coagulation. A rapid deterioration of the prothrombin time at an early stage is an index of a poor prognosis. The stools may contain occult or macroscopic blood. The volume of the urine is reduced and it contains bilirubin and urobilinogen; proteinuria is common. White blood cell counts vary from leucopenia to leucocytosis. Blood cultures, which should be undertaken frequently, may reveal septicaemia. Hypoglycaemia, hypokalaemia and disturbances of acid-base balance may also occur.

Treatment. There is no specific therapy. Supportive treatment is discussed on page 552.

Differential Diagnosis of Acute Parenchymal Disease of the Liver

The differential diagnosis of the various types of acute parenchymal disease is not difficult in the majority of cases. When a young person develops jaundice, preceded by gastrointestinal upset, and associated with pale stools and dark urine, the presumptive diagnosis is infective hepatitis. A history of recent contact with a case of jaundice makes this more certain. A history of transfusion or injection or damage to the skin while handling blood suggests the diagnosis of serum hepatitis; this is supported by the demonstration of HAA in the patient's serum. Acute over-indulgence in alcohol may give a similar clinical picture.

Infectious Mononucleosis. The pre-icteric phase of viral hepatitis may be confused with other acute infective diseases and in particular, in young people, with infectious mononucleosis. In the latter condition there is enlargement of the lymph nodes and a typical blood picture. Later the Paul-Bunnell reaction becomes positive in high dilutions.

Bacteraemia. Hepatitis and hepatic cell necrosis may accompany septicaemia, particularly with organisms such as *Esch. coli.* When this occurs the patient is profoundly ill and febrile and the diagnosis is confirmed by blood cultures.

Acute Massive Necrosis. This condition should be suspected if there is a history of exposure to a known hepatotoxic agent. In the absence of such a history, the severity of the illness, the depth of the jaundice, and the development of lethargy and coma suggest that massive necrosis has occurred.

Weil's Disease. In a typical case of leptospirosis of moderate severity, the onset is abrupt and haemorrhages, e.g. epistaxes and petechiae, are common: these are less common in viral hepatitis. Weil's disease is associated with leucocytosis, and blood and casts are found in the urine; in viral hepatitis leucopenia occurs, the urine is usually normal and the SGPT much higher. The patient with Weil's disease is likely to give a history of occupational exposure to infection, and diagnosis can be confirmed by appropriate bacteriological methods.

Obstructive Jaundice. The most difficult problem in diagnosis is the differentiation between the jaundice of viral hepatitis and extrahepatic obstructive jaundice due to a 'silent' stone in the common bile duct or to obstruction of this duct by neoplasm, especially if the jaundice in viral hepatitis persists without marked improvement for more than three weeks. The distinction is made more difficult by the knowledge that in many patients with viral hepatitis the effect on the liver is predominantly one of intrahepatic stasis in bile ducts rather than parenchymal cell necrosis. Fever may be present in both types of jaundice, in the one as a result of virus infection, and in the other as a result of ascending cholangitis (p. 562). It is particularly important to make a correct diagnosis since the operative interference which is indicated in extrahepatic obstructive jaundice may have serious effects in cases of infective hepatitis and other types of hepatocellular jaundice. Radiographs of the abdomen should be taken in every case. They are helpful when radio-opaque stones are seen in the gall-bladder or common bile duct and more rarely in showing calcification of the pancreas following pancreatitis. In the absence of these findings, repeated liver function tests (p. 534) become of great value. The initial determinations should be performed as early in the course of the jaundice as possible and the decision to operate should be determined largely by them when the clinical picture is equivocal. In obstructive jaundice the serum alkaline phosphatase is rarely less than 30 KA units and SGPT rarely more than 100 units/ml, while in jaundice due to hepatocellular disease alkaline phosphatase values tend to be less than 30 KA units, while SGPT values often reach several hundreds of units per millilitre. In those cases in which the clinical picture, liver function tests and immunological studies are indeterminate, liver biopsy, carried out by liver puncture under local anaesthesia often provides evidence upon which an accurate diagnosis may be based. In occasional patients cholangiography may be helpful but there are always a few patients in whom persistent obstructive jaundice demands a laparotomy after three to four weeks if investigation gives equivocal results.

Treatment of Acute Parenchymal Disease of the Liver

BED REST. This is best imposed until evidence of activity has subsided. The appetite should have improved, enlargement and tenderness of the liver on palpation should have disappeared and normal colour should have returned to the stools before the patient is allowed up other than for brief periods.

For the average case of infective hepatitis this usually involves two to three weeks bed rest. Slight persistent jaundice (plasma bilirubin $< 1{\cdot}5$ mg/100 ml) is not by itself an indication for continued confinement to bed. It will be impossible to adhere to these criteria in the few cases in whom activity of the disease process continues for months or years. Because of the known modes of spread of viral hepatitis strict hygiene must be observed by the patient and his attendants and special care is necessary in handling laboratory specimens and disposing of excreta.

DRUGS. Those which are known to be inactivated by the liver are best avoided or used in reduced dosage. Not only are they all potential hepatotoxic agents but some, e.g. morphine and barbiturates may confuse the clinical picture in those patients showing cerebral disturbance. Abstinence from alcohol should be advised for at least six months. The contraceptive pill should not be used for a similar period.

DIETARY REGIME. (*a*) *In mild and moderately severe cases.* The best results are probably obtained by giving a diet of 3,000 calories from the onset of the disease and for several weeks after the acute symptoms have subsided. A similar diet is recommended for cirrhosis of the liver and the basis of its construction is given in Diet 11 (p. 1001). Owing to nausea and malaise many patients are unable to tolerate such a high energy diet in the first few days of acute parenchymal disease. In these circumstances a light diet supplemented with carbohydrate in the form of fruit drinks and glucose will be found to be acceptable. The actual content of the diet should be largely dictated by the patient's desires; the high energy diet, rich in protein, however, should be given as soon as possible. In the great majority of cases complete recovery occurs within a few weeks and the patient may be allowed a normal diet. In the small proportion in whom the activity of the disease persists for months or years the diet should be continued but in those who can tolerate fat its prolonged restriction is neither justified nor desirable.

(*b*) *In severe cases.* In a few cases of viral hepatitis and Weil's disease and in almost all cases of massive liver necrosis, the patient is seriously ill and is unable to ingest an adequate amount of food because of nausea or vomiting. The mentality is clouded or the patient may be in coma, and the neurological manifestations of severe parenchymal failure may be present (p. 550). In the presence of such features nitrogen-containing foods and supplements, i.e. all proteins, should be prohibited.

The best results are obtained by giving glucose by stomach tube or intravenous infusion. A 10 to 20 per cent solution of glucose may be delivered into a large peripheral vein through a polythene tube and up to 300 g of sugar may be given in the course of the day. The amount of saline used as carrier for the glucose should be evaluated from day to day, taking into account the urinary output and the state of electrolyte balance. Parentrovite Forte, which is a high-potency mixture of B vitamins and ascorbic acid, is added to the fluid prior to its administration, or can be given by separate intravenous or intramuscular injection. Thiamin (20 mg/day) should be added to the fluid prior to its administration, and potassium salts may be given orally.

ADDITIONAL MEASURES. Even in the absence of protein feeding the bacterial flora in the gut appear to contribute to the clinical picture, probably by producing toxic nitrogenous compounds. Because of this, oral neomycin, 1 g six-hourly, is recommended, and evacuation of the colon by daily enema is advised initially.

Excitement and restlessness during episodes of confusion are best controlled by intravenous injections of diazepam (5 mg).

Because there is usually a haemorrhagic diathesis, intramuscular injections are best avoided. Fresh blood or appropriate coagulation factors may also be required if bleeding occurs or if the prothrombin time becomes excessively prolonged.

When a *severe* case of hepatitis shows deterioration despite the above measures, large doses of either hydrocortisone (100 mg) or tetracosactrin (0.5 mg every 48 hours) are administered but their value is not established.

In those who improve and can tolerate food by mouth, protein should once more be included in the diet. It is advisable to start with no more than 25 g per day, the amount being slowly increased to about 40 or 50 g per day. It is usually found that patients who survive hepatic coma or who have had the neurological signs attributable to nitrogenous intoxication are unable to tolerate much more than 50 g of protein per day.

Patients who proceed rapidly into coma from massive liver necrosis and who are unresponsive to the foregoing measures have a mortality in the region of 90 per cent. Exchange transfusion does not appear to improve this figure and in cases of viral hepatitis it carries the serious risk of cross-infection. Extracorporeal circulation of the patient's blood through pig, monkey or cadaver liver and charcoal haemoperfusion are being studied as possible means of supporting the patient until his own liver begins to recover.

CHRONIC PARENCHYMAL DISEASE

Classification and Pathology. Chronic parenchymal disease is subdivided into (1) chronic hepatitis which is characterised by chronic inflammatory changes, and (2) cirrhosis of the liver in which fibrosis is most conspicuous.

1. CHRONIC HEPATITIS. (i) *Chronic Persistent Hepatitis.* Inflammatory changes are confined to the portal tracts and the hepatic architecture remains intact. There is no progression to cirrhosis.

(ii) *Chronic Aggressive Hepatitis.* This condition is characterised by inflammatory infiltration of the portal tracts and adjacent parenchyma and by necrosis of hepatocytes at the junction of the two ('piecemeal necrosis'). There is also intralobular fibrosis with distortion of hepatic architecture. Cirrhosis usually develops.

2. CIRRHOSIS OF THE LIVER. This is a generic term applied to chronic diffuse liver disease of multiple aetiology, characterised by destruction of parenchymal cells, distortion of the normal lobular architecture with nodular regeneration of the parenchymal cells and overgrowth of fibrous tissue. There are three basic pathological types of cirrhosis:

(i) *Diffuse Hepatic Fibrosis* (*Portal Cirrhosis*). This appears to occur as a sequel to two kinds of lesion: (*a*) infiltrative disease of the liver without previous necrosis, the most common example of which is fatty infiltration of the liver, and (*b*) zonal necrosis, following which fibrosis may rarely occur if complete restoration of tissue is prevented either by repeated episodes of necrosis, e.g. repeated attacks of infective hepatitis, or by chronic interference with cell nutrition or oxygenation, e.g. in malnutrition or chronic heart failure. Every lobule is involved in the fibrosis, which begins around the central veins and the portal tracts. As a result of the diffuse regenerative hyperplasia, the organ becomes finely granular. Depending on the stage of the process and the degree of infiltration, the organ is increased, normal or diminished in size.

(ii) *Post-necrotic Scarring*. Post-necrotic scarring occurs in livers which have been the seat of massive hepatic necrosis. The collapse of the reticulin framework of the liver lobules which follows the removal of the dead cells in massive necrosis permits extensive development of fibrous tissue in wide bands throughout the liver. Areas of relatively normal hepatic tissue remain as islets, and from these grow new hepatic cells which do not assume the normal lobular arrangement, producing an organ which is grossly and irregularly nodular.

(iii) *Biliary Cirrhosis*. In the majority of cases biliary cirrhosis occurs as a result of biliary obstruction and superimposed infection, i.e. cholangitis and cholangio-hepatitis. *Esch. coli* and *Strep. viridans* are the most common infecting organisms. Distension of the bile canaliculi, proliferation of the bile ducts in the portal tracts and degeneration and inflammatory infiltration of the parenchyma around the portal tracts result in a diffuse fibrosis which is predominantly portal and periportal. Parenchymal cell regeneration is usually marked. The fibrosis spreads and classically surrounds single lobules or groups of lobules. Fibrosis around the central vein is less marked than in portal cirrhosis.

The term *primary biliary cirrhosis* is used to describe a chronic non-suppurative pericholangitis of unknown origin, without evidence of infection occurring mainly in middle-aged females and often associated with autoimmune disturbances.

Aetiology of Chronic Parenchymal Disease. DIET. Experimental work on animals has shown that cystine, tocopherol and selenium deficiency can lead to acute massive necrosis, but it seems improbable that these factors are implicated in the aetiology of post-necrotic scarring in human subjects. Diffuse fatty infiltration of the liver can be produced experimentally in animals by diets deficient in protein and certain food constituents, which, because of their power to remove neutral fat, are termed lipotropic substances. These substances include choline, inositol and methionine. Methionine probably acts by virtue of possessing a labile methyl group needed in the synthesis of choline. Infiltration of the liver with fat may thus be regarded as a result of a deficiency of labile methyl groups. Whether directly as a result of fatty infiltration, or because of hepatic cell damage or an associated metabolic defect, diffuse fibrosis occurs around both the central veins and portal tracts (portal cirrhosis). In man, however, the evidence for a relationship between fatty infiltration and cirrhosis is not well documented. Many conditions associated with a fatty liver are so regularly accompanied by cell necrosis that the role of uncomplicated fatty infiltration cannot be clearly defined. The incidence of chronic liver disease after kwashiorkor (p. 118) and other conditions associated with fatty infiltration is not significant.

ALCOHOL. Acute alcoholic intoxication can produce parenchymal cell damage and an increase in the fat content of liver cells. In addition many chronic alcoholics eat a diet deficient in protein and lipotropic food factors, and since their energy intake derived from alcohol is usually large, there results a disparity between the intake of energy and of essential food factors. Both factors result in fatty infiltration, which appears to be a precursor of diffuse hepatic fibrosis. In some cases iron is laid down in the parenchymal cells of the liver due to the increased absorption of iron from the alimentary tract which occurs in the presence of alcohol and to the high iron content of many alcoholic beverages. A history of chronic alcoholism is frequently present in cases of diffuse hepatic fibrosis occurring in Britain. The association is even more commonly encountered in France, the United States and South Africa; many patients with alcoholic cirrhosis vehemently deny an excessive intake of alcohol.

INFECTION. Acute infective hepatitis and serum hepatitis are the most common infective diseases of the liver in Britain, and are usually followed by complete recovery. About one-third of the cases of cirrhosis, however, give a history of previous episodes of jaundice which was apparently neither obstructive nor haemolytic. In severe cases of viral hepatitis characterised by massive necrosis in which death does not occur, post-necrotic scarring is inevitable. Diffuse hepatic fibrosis (portal cirrhosis) appears also to follow viral hepatitis; it is possible that repeated attacks of zonal necrosis are necessary for this development to take place. Such patients follow a relapsing course due to the chronic aggressive hepatitis.

IMMUNE REACTIONS. It has been suggested that liver cell damage in Australia antigen-positive patients may be related to a cell-mediated immune response (p. 35). It is postulated that if this is normal, acute hepatitis resolves as the antigen is removed. If the immune response is impaired, the antigen persists causing chronic aggressive hepatitis. If there is no immune reaction, the antigen persists without causing liver damage.

Primary biliary cirrhosis is often associated with autoimmune disease, such as Hashimoto's thyroiditis, and with a high titre of antibodies to mitochondrial and nuclear components.

OBSTRUCTION OF THE BILE DUCTS. Long-standing obstruction of the bile ducts, associated with an ascending cholangitis, usually leads to biliary cirrhosis. In most cases obstruction is extrahepatic in situation, e.g. stone in the common bile duct. This is followed by an ascending infection of the biliary tree which results in a variable degree of intrahepatic inflammatory biliary obstruction. Such cholangio-hepatitis may lead to the development of biliary cirrhosis even if the extrahepatic obstruction is removed. Rarely biliary cirrhosis may develop from cholangio-hepatitis which has arisen in the absence of extrahepatic biliary obstruction. In some of these cases the infection may start *de novo*, while in others it may be initiated by obstruction to the intrahepatic biliary tree, e.g. by stones or duct tumours.

CHRONIC CARDIAC FAILURE. Diffuse hepatic fibrosis following centrilobular degeneration and necrosis occurs occasionally as a result of long-standing heart failure. It is most frequently associated with mitral stenosis, tricuspid regurgitation or chronic constrictive pericarditis.

HEPATIC INFILTRATIONS. Substances infiltrating the hepatic parenchymal or connective tissue have been shown to be associated with diffuse hepatic fibrosis. Fatty infiltration has already been discussed in relation to alcohol and dietary deficiency of protein and lipotropic substances. It is also found commonly in diabetic subjects. Excessive glycogen infiltration occurring in children from birth in von Gierke's disease leads to diffuse fibrosis. Gaucher's disease, Niemann-Pick disease and xanthomatosis also produce hepatomegaly due to infiltration of the reticulo-endothelial cells in the liver by kerasin, sphingomyelin and cholesterol respectively; diffuse fibrosis ensues. Amyloid disease, which involves the walls of the sinusoids, occasionally results in diffuse hepatic fibrosis. Wilson's disease in which there is an abnormal accumulation of copper in the liver, is associated with hepatic fibrosis. In haemochromatosis and in Bantu siderosis (p. 128) iron is absorbed in large amounts from the alimentary tract and deposited both in the liver parenchyma and in the cells of the reticulo-endothelial system. In the liver, cell degeneration and diffuse fibrosis develop.

CRYPTOGENIC. In many cases of cirrhosis of the liver all investigations fail to reveal any aetiological factor.

Chronic Hepatitis

Chronic Persistent Hepatitis

This condition may be no more than a variant of a viral hepatitis in which the disease runs a protracted course. The ultimate prognosis is good and in this regard the term 'persistent' is misleading. Corticosteroid therapy is not of value.

Chronic Aggressive Hepatitis

(CHRONIC ACTIVE HEPATITIS; ACTIVE CHRONIC HEPATITIS; LUPOID HEPATITIS; JUVENILE CIRRHOSIS)

Clinical Features. The relationship of this condition to infective hepatitis is not well defined. The onset is usually insidious, but it may present as a typical acute hepatitis with the correct diagnosis being established only with hindsight later in the course of the disease. In addition to the stigmata of chronic liver insufficiency (p. 559) there is hepatosplenomegaly, often with evidence of multisystem involvement, e.g. arthralgia, skin rashes and endocrine disturbances. Pyrexia may be prominent.

Laboratory findings include high levels of gamma-globulins, particularly IgG.

Disturbance of the immune mechanisms is also indicated by positive ANF, WR, Rose-Waaler test, Coombs' test and smooth muscle antibody test. LE cells can be demonstrated in some patients. The progress of the disease can be considerably improved by corticosteroid therapy. If not, an immunosuppressive agent, such as azathioprine, may be tried.

Cirrhosis of the Liver

1. Diffuse Hepatic Fibrosis

(Portal Cirrhosis)

Clinical Features. This condition is more common in men. It may be entirely latent during life and discovered only at post-mortem examination. In some cases, the incidental finding of a firm palpable liver may be the first indication of the disease. The hepatomegaly which is common in the early stages of cirrhosis results from fatty infiltration or parenchymal hyperplasia. The organ has a smooth edge, and is not tender. Later, with increased fibrosis and parenchymal destruction, the liver shrinks and becomes smaller than normal. The main clinical features of the condition are attributable to portal hypertension, hepatic insufficiency, or a combination of both.

1. PORTAL HYPERTENSION. Elevation of hydrostatic pressure in the portal system occurs as a result of partial obstruction to the flow of portal venous blood through the liver. This is probably due to fibrosis, which decreases the vascular bed and distorts the vascular tree, and to transmission of hepatic arterial pressure to the portal venous system. As a consequence of portal hypertension, there develop features related to the gastrointestinal tract, haemopoietic system, spleen, portal vascular tree and abdominal cavity.

(i) *Vague digestive complaints* are frequent in the initial stages of the disease and result from congestion of the gastrointestinal tract. They include flatulence, nausea, anorexia and vomiting, especially in the morning. Later, pain in the right hypochondrium occurs, usually after meals. Abdominal distension is common and is due to impaired intestinal gaseous absorption and to ascites. Anorexia aggravates the poor nutritional state usually already present. In those with an alcoholic history, polyneuropathy, rough skin and smooth tongue are not infrequently present.

(ii) *Splenomegaly* is a primary result of portal hypertension. In addition to the factor of congestion, hyperplasia of the reticulo-endothelial cells of the spleen occurs as a direct consequence of hepatic damage. The mechanism of this is uncertain. The organ is usually hard, but only moderately enlarged except in children in whom it may be considerably increased in size.

(iii) A *collateral circulation* appears wherever there is communication between portal and systemic veins. These sites are at the lower end of the oesophagus and the upper end of the stomach, the anus and lower rectum, at the normally obliterated embryological circulation through the falciform ligament, and between colon, omentum and spleen and the retroperitoneal veins. Oesophageal and gastric varices are common and their rupture, producing haematemesis, may be fatal. A haematemesis may be the first sign in a hitherto unsuspected case of hepatic cirrhosis. The demonstration of the presence of oesophageal varices from the mucosal pattern following a barium swallow or by oesophagoscopy is a valuable means of substantiating the diagnosis of hepatic cirrhosis or detecting the cause of unexplained melaena, occult blood in the stools, frank haematemesis or splenomegaly. Haemorrhoids developing in a middle-aged person for no obvious reason, or the appearance of large veins in the abdominal wall and around the umbilicus, should arouse suspicion that cirrhosis of the liver is present.

The injection of a radio-opaque substance into the spleen (transcutaneous splenovenography), direct injection into the superior mesenteric artery by coeliac artery catheterisation or into the portal vein by cannulation of a patent umbilical vein may be used in selected patients to demonstrate the extent of collateral venous channels and to determine the patency of the splenic and portal veins.

(iv) *Anaemia*, hypochromic and microcytic, or, more rarely, normochromic and macrocytic, occurs. The former is usually due to blood loss. The latter is very rarely associated with a megaloblastic reaction in the marrow, which may be due to an associated nutritional folate deficiency or to lack of intrinsic factor from gastritis and consequent malabsorption of vitamin B_{12}. An associated moderate thrombocytopenia and leucopenia may be present, and these are generally attributed to concomitant hypersplenism (p. 756).

(v) *Ascites* is commonly, though not invariably present, in cases of hepatic cirrhosis. It is usually associated with, but is out of proportion to ankle and lower limb oedema. There are probably several factors responsible for water and salt retention and ascites in hepatic disease; these include (1) a lowering of the osmotic pressure of the plasma as a result of failure of the liver to synthesise albumin; (2) portal hypertension and lymphatic obstruction produced by the fibrosis in the liver substance which may be responsible for the localisation of most of the retained fluid in the peritoneal cavity; (3) failure on the part of the liver to inactivate aldosterone and vasopressin. These lead to excessive reabsorption of salt and water in the tubules of the kidney; and (4) a lowering of the glomerular filtration rate, which is probably responsible for excessive tubular reabsorption of salt and other electrolytes.

2. HEPATIC INSUFFICIENCY. The principal clinical features of hepatic insufficiency are the following:

(i) *Jaundice*. This is rarely severe and is present in only a minority of cases, usually in the terminal stages of the disease. It occurs as a result of parenchymal cell damage (hepatocellular jaundice) and intrahepatic obstruction to bile canaliculi. In cirrhosis associated with alcoholism recurrent bouts of superimposed acute toxic hepatitis are caused by alcoholic excesses.

(ii) *Oedema*. This is probably the result of a fall in plasma colloid osmotic pressure and of the hormonal factors discussed above, and is to be regarded as evidence of hepatic failure.

(iii) *Spider Angiomata, Capillary Dilatations in the Skin (Telangiectases), Erythema of the Palms and Hypogonadism*. These features are frequently seen, and are believed to be produced by an excess of circulating oestrogens, which probably results from the failure of the damaged liver to inactivate them. The spider angiomata occur predominantly on the forehead, neck, forearms and the hands. In the male oestrogen excess may occasionally produce hypogonadism, i.e. female distribution of hair, gynaecomastia and testicular atrophy.

(iv) *Cyanosis, Hyperdynamic Circulation and Finger Clubbing.* These features are seen in a few patients. The most likely explanation is veno-arterial shunting of blood in multiple pleural and intrapulmonary telangiectases.

(v) *Generalised Haemorrhagic Tendency.* This occurs only in advanced cirrhosis of the liver and is largely due to prothrombin, factor VII and factor IX deficiency. Thrombocytopenia due to hypersplenism, if marked, is a contributory factor. In occasional patients there is also abnormal fibrinolysis. Epistaxis, purpura, menorrhagia or melaena may develop.

(vi) *Generalised Pigmentation of the Skin.* This is due mainly to increased deposition of melanin in the skin, and occurs in a minority of cases. It may be related to a disturbance of amino acid (tyrosine) metabolism.

(vii) *Dupuytren's Contracture.* This deformity of the hand is occasionally seen in hepatic cirrhosis in which alcoholism is a prominent feature of the history.

(viii) *Hepatic Encephalopathy* (*Portal-systemic Encephalopathy*). The severe mental changes progressing to coma and the neurological features which have been described in relation to acute massive necrosis (p. 550) occur also in patients suffering from hepatic cirrhosis. However, these features usually tend to be more chronic and intermittent. In addition to the factor of severe parenchymal cell failure, the presence of collateral venous circulation by-passing the liver permits certain nitrogenous compounds absorbed from the intestine to enter the systemic circulation directly and so produce the abnormal behaviour and the neurological features. The condition is easily precipitated in a susceptible patient by the giving of CNS depressants and nitrogen-containing foods: it tends to improve if the bowel is emptied or sterilised. Neuropsychiatric complications may overshadow the associated liver disease. This may lead to the patient's being admitted to a mental hospital because of the incorrect diagnosis of primary mental disorder. If the anastomotic channels are extensive these features may occur even in the presence of relatively good hepatic cell function and in the absence of jaundice. This is a particularly unfortunate but not uncommon sequel to the operation of portacaval anastomosis.

Encephalopathy may also follow gastrointestinal bleeding, infection or hypokalaemia. After bleeding, anaemia and hypotension may cause further liver damage, and the blood reaching the colon provides a protein substrate for bacterial action and nitrogen production.

Course and Prognosis. In the absence of haematemesis or melaena the prognosis of cirrhosis of the liver depends upon the degree of hepatic damage and upon the intensity with which modern treatment is applied. Some patients may realise their full life expectancy and it is no longer correct to accept a relentless downhill course as inevitable. Bad prognostic signs are those of gross hepatic insufficiency and severe portal hypertension, leading to repeated haematemeses. Death occurs from bleeding varices in about 20 per cent of cases. Intercurrent infection is a common terminal event, and death in hepatic coma from severe hepatic insufficiency accounts for a further group of fatal cases. There is also an increased incidence of hepatoma in subjects with cirrhosis.

Laboratory Data. The concentration of plasma albumin is reduced. A rise occurs in plasma globulin concentration, so that the total protein concentration may be little altered. The changes that occur in the immune globulins are not sufficiently specific to be discriminative. Tests for impaired parenchymal cell functions (p. 536) are positive in the majority of cases. The tendency to bleed is little affected by vitamin K administration. SGPT is commonly slightly elevated to 100 units/ml. Serum alkaline phosphatase concentration is usually increased to 20-30 KA units per 100 ml. In those patients who show no disturbance of liver function in routine tests, estimation of bromsulphthalein excretion is valuable since this is usually impaired.

In contradistinction to these positive findings of abnormal parenchymal cell metabolism, tests of bile pigment excretion are minimally affected. Plasma bilirubin is usually only slightly increased and, except in advanced cases, there is no bilirubin in the urine, though urobilinogen is almost invariably present. The stools are not pale and contain normal amounts of stercobilinogen.

Differential Diagnosis and Treatment. See pages 563 and 563 to 566 respectively.

Post-necrotic Scarring

Post-necrotic scarring is less common than diffuse hepatic fibrosis. In the vast majority of cases it is a sequel to a previous recognisable attack of acute massive necrosis of the liver. In these cases, a history of jaundice is invariable, and one of repeated episodes of jaundice over the preceding years is frequent. In a minority of cases of post-necrotic scarring, there is no history of a previous attack of acute liver damage with jaundice. It is possible that in these cases the necrosis is less acute, and takes place over a longer period of time.

Clinical Features. The liver is enlarged early in the disease, and in some cases the edge is grossly irregular and feels similar to that in metastatic hepatic neoplasm. The clinical features and laboratory evidence of hepatic insufficiency are similar to those found in diffuse hepatic fibrosis (portal cirrhosis), but they occur earlier in the course of the disease. Accordingly the differential diagnosis from portal cirrhosis may be difficult and from a therapeutic point of view is of little importance. The disease is, however, more common in women and a history of alcoholism is usually not present. The tendency to early development of liver insufficiency makes the prognosis of post-necrotic scarring poorer than that of portal cirrhosis.

Treatment. This is described on pages 563 to 566.

Cholangio-hepatitis and Biliary Cirrhosis

Clinical Features. Biliary cirrhosis, a rare condition, is more common in women than in men and usually begins with a phase of extra- or intrahepatic obstructive jaundice, which may or may not be associated with pain, depending on the nature of the obstruction (p. 540). The obstruction may be partial or complete and this accordingly determines the degree of jaundice, which may even be absent. Usually the stools are pale, and the urine dark from the presence of bilirubin. The liver is uniformly enlarged and smooth, and the spleen is not usually palpable. Flatulence, nausea and severe pruritus may be present.

Cholangitis and cholangio-hepatitis complicate gall-stone obstruction and bile duct stricture but not carcinoma of the head of pancreas. Infection manifests itself by the presence of the following features. Fever is usual but not invariable. It may be recurrent over many weeks or months. Hepatic enlargement may increase with febrile episodes, and be associated with upper abdominal pain. Jaundice fluctuates and becomes more intense as fever increases. With these febrile episodes and deepening jaundice, pruritus, anorexia, flatulence and vomiting increase. In severe cases, rigors, prostration and a hectic temperature, similar to that of septicaemia, occur. Indeed in a few patients positive blood cultures can be obtained. A polymorphonuclear leucocytosis is frequently present, but severe infection can occur with leucopenia. Finger clubbing is common and xanthomata may eventually appear in the skin. Bone pain develops due to osteomalacia.

Biliary cirrhosis becomes established after months or years of such chronic infection and obstruction. Ascites and the signs and symptoms of portal hypertension are much less common than in either portal cirrhosis or post-necrotic scarring and may be absent throughout the whole course of the disease. In the early stages, the clinical picture of obstructive biliary cirrhosis may be similar to that of post-necrotic scarring with jaundice. In the later stages, due to the absence of bile salts from the small bowel, features of malabsorption and steatorrhoea dominate the clinical picture.

Course and Prognosis. Biliary cirrhosis may be prevented in patients in whom prompt surgical removal of the obstruction to the biliary passages is possible. If this is not done, or if the obstruction is intrahepatic, continuing liver damage is inevitable and the patient will probably survive for not more than four or five years. Jaundice is a prominent feature over this period and death usually occurs from hepatic insufficiency or more rarely from the bleeding of varices due to secondary portal hypertension.

Primary Biliary Cirrhosis

Primary biliary cirrhosis affects predominantly middle-aged females. There is no previous history of biliary surgery. Pain, fever and rigors do not occur. Pruritus is the commonest initial complaint and may precede the appearance of jaundice by many months. Laboratory studies show elevated levels of alkaline phosphatase, cholesterol and phospholipid and the hyperlipaemia may be associated with xanthomatous deposits around the eyes, in skin creases and over pressure areas. In addition to hepatomegaly, the spleen becomes enlarged and as the disease progresses the patient develops a deep bottle-green jaundice. The condition usually proves fatal within five to ten years, either from liver failure or alimentary bleeding.

The diagnosis is suggested by the clinical picture, the biochemical features, a positive serum mitochondrial antibody test and elevated IgM levels and can usually be confirmed by liver biopsy. In the early stages it may be possible to define the biliary tract by cholangiography, but often a laparotomy is necessary to exclude any extrahepatic obstructive lesion.

Differential Diagnosis of Cirrhosis of the Liver

The differential diagnosis includes consideration of other causes of chronic dyspepsia (p. 460) and haematemesis (p. 464). When enlargement of the liver is present, the following should be considered:

1. Chronic cardiac failure. The liver is large and smooth, frequently tender and may pulsate if there is tricuspid regurgitation; it is less hard than the cirrhotic liver. Other manifestations of cardiac failure are present.
2. Secondary carcinoma of the liver. Irregular nodules may be palpable or the liver may be diffusely enlarged and hard. There is seldom splenomegaly. Peritoneal involvement produces ascites which may be haemorrhagic and contain tumour cells. The primary tumour may be discovered.
3. Rarer causes of enlargement of the liver in Britain are primary carcinoma of the liver, Hodgkin's disease, leukaemia, amyloid disease, sarcoidosis, amoebic abscess and hydatid cysts. In tropical countries hepatomegaly is frequently associated with kala-azar, malaria and schistosomiasis.
4. The cirrhosis of infiltrations of the liver such as haematochromatosis and hepato-lenticular degeneration are characterised by the other features of these diseases.

If consideration of the clinical features and laboratory tests fails to establish the diagnosis in a case of hepatomegaly, it may be necessary to obtain a biopsy specimen either at laparotomy or by aspiration.

Treatment of Cirrhosis of the Liver

Diffuse Hepatic Fibrosis and Post-necrotic Scarring. There is no doubt that adequate medical treatment can influence the prognosis of cirrhosis of the liver by favouring hyperplasia of the parenchymal cells, by preventing further progression of the fibrosis, by increasing the hepatic reserve and by inhibiting the development of fluid retention and encephalopathy. This is especially so in cases of diffuse hepatic fibrosis. Medical measures do not influence established portal hypertension, so that haematemesis cannot be prevented by such means. The main therapeutic problems are correction of malnutrition, treatment of fluid retention, control of alimentary bleeding due to portal hypertension and the management of encephalopathy.

1. *Nutrition.* It is generally agreed that dietary deficiency plays a part in the genesis of some cases of hepatic cirrhosis. As a result, a high energy diet (approximately 3,000 calories per day) which is rich in protein (120 g), and which contains approximately 400 g carbohydrate, is recommended except for those patients who are showing evidence of early encephalopathy. When jaundice is absent a fat intake of 100 g per day can be given to most cases of cirrhosis of the liver. Positive nitrogen balance may be obtained by these diets and improvement in hepatic function may be shown over periods of months, by an increasing albumin concentration in the blood and by other liver function tests. When oedema or ascites is present it may be desirable to replace 20-40 g of protein in the diet by Casilan, given in water or milk. This preparation of milk protein is particularly useful because it is nearly salt-free and facilitates

the provision of a high protein diet low in salt (Diet 12, p. 1002). Alcoholic drinks must be forbidden.

Other dietary supplements which have been used, and for which there is theoretical justification, include yeast, thiamin, niacin, riboflavin, choline and the sulphur-containing amino acids, methionine and cystine. A moderate intake of thiamin, niacin and riboflavin is ensured by the protein-rich diet recommended above. Nevertheless additional daily supplements should be given orally, yeast $\frac{1}{4}$-$\frac{1}{2}$ oz., thiamin 5 mg, niacin 50 mg and riboflavin 5 mg per day representing adequate amounts. In practice, methionine and choline are rarely prescribed in this condition because of their expense and because there is reason to believe that the body can be supplied with adequate amounts of these substances if a high protein diet containing ample quantities of milk is taken.

2. *Fluid Retention.* Ascites and oedema may respond to the improvement in hepatic function brought about by the above measures. As a first step the patient may be allowed salt in cooking but be forbidden soups, ham, bacon and salt at the table. This will reduce his intake to about 2 g of sodium per day. If further salt restriction is necessary a special 0·5 g sodium diet should be prescribed (Diet 8, p. 998). Frusemide, ethacrynic acid and thiadiazine diuretics are all effective but should be used with care, since they frequently aggravate or precipitate hepatic encephalopathy probably from causing or aggravating hypokalaemia. Potassium supplements (p. 191) should therefore be prescribed. Amiloride (p. 196) is less liable to cause potassium depletion. The specific aldosterone antagonist, spironolactone, may be given in addition in a dose of 25 mg four times per day in severe cases.

A small number of patients with ascites and oedema are found to be resistant to all the therapeutic measures discussed above. For such cases the intravenous administration of salt-poor albumin preparations (25 g) given in 5 per cent dextrose solution or osmolar loading with an intravenous infusion of mannitol may promote diuresis. Abdominal paracentesis inevitably removes proteins and electrolytes in the ascitic fluid and is contraindicated except for diagnostic purposes and in the few patients who cannot be kept comfortable in any other way.

3. *Bleeding from Oesophageal and Gastric Varices.* Blood transfusion is necessary when haematemesis or melaena is sufficiently severe to produce a state of shock or significant anaemia. If bleeding continues the patient should receive 20 units of vasopressin in 100 ml dextrose over a period of 10 minutes; this acts by reducing portal venous pressure consequent on mesenteric vasoconstriction. The dose may be repeated every two hours. Should haematemesis still persist then bleeding may be controlled by using a Sengstaken tube. This tube possesses two balloons which when inflated exert pressure both in the fundus of the stomach and in the lower part of the oesophagus. If bleeding continues emergency surgery is necessary. The favoured operation is ligation of the varices at the lower end of the oesophagus by a transthoracic approach.

In those patients who have chronic bleeding from varices or who survive acute haemorrhage, elective surgery offers the only hope of reducing portal hypertension. As the block is in the liver, splenectomy alone will not be effective. Blood must be shunted from the portal to the systemic circulation by anastomosing the splenic vein after splenectomy to the left renal vein, or the portal vein to the inferior vena cava. The latter procedure is more effective. It has also been suggested that haemorrhage may be prevented by resecting the area of varices at the lower end of the oesophagus and the upper end of the stomach. Such surgical procedures are difficult to perform and carry a considerable risk to life. These major operations are indicated when the risk of death from haemorrhage is greater than the risk of death from liver failure. They should not be undertaken if hepatic cell function is very severely diminished or if ascites cannot be controlled by medical measures. Even in selected patients the results of surgery, while reducing bleeding, are often disappointing because of the development of encephalopathy and progression of the underlying liver disease.

In the general management of patients with oesophageal and gastric varices, salicylates should be forbidden since they may precipitate bleeding. Iron therapy may be required from time to time to deal with iron deficiency anaemia.

4. *Hepatic Encephalopathy*. The episodic confusion which punctuates the course of many patients with cirrhosis of the liver is usually reversible; when coma supervenes this is usually a terminal event and consciousness can be restored in only about 10 per cent of cases.

The principles of treatment are similar to those described for the encephalopathy complicating massive liver necrosis (p. 553). All protein is prohibited and 10 to 20 per cent glucose is given intravenously so that the patient receives about 1,500 calories per day. Parentrovite Forte, thiamin and neomycin are also prescribed. Any obvious precipitating factor such as haemorrhage, infection or hypokalaemia is treated promptly.

When the patient begins to recover, fruit drinks with added glucose are given by mouth and then feeding begins with a diet which contains 25-30 g of protein daily. This amount of protein is gradually increased to the maximum that the patient can tolerate, usually 40-60 g per day. This is judged on the basis of intellectual function and sometimes with the help of serial electro-encephalographic changes. Neomycin is continued in a dose of 2 g per day. The patient is instructed to try and maintain daily bowel movement with the aid of a laxative, e.g. Senokot, if necessary.

If the patient fails to keep well, lactulose should be tried in addition to neomycin; it is not absorbed from the intestine and promotes the growth in the colon of starch-splitting bacteria at the expense of protein-splitting bacteria. The change in bacterial flora and fall in pH reduces the production and absorption of nitrogenous compounds from the bowel with good effect in some patients. The dose of lactulose is 15 ml t.i.d. increasing to 30 ml t.i.d.

Biliary Cirrhosis and Cholangio-hepatitis. Biliary cirrhosis can be prevented in a proportion of cases by prompt surgical treatment of obstructive jaundice. Laparotomy should be carried out in all cases with features of obstructive jaundice if the jaundice does not subside within a few weeks, unless there is good reason to believe that the patient has acute parenchymal disease of the liver with superimposed intrahepatic obstruction. When no obstruction to the extrahepatic bile ducts is found at operation, treatment is unsatisfactory and largely symptomatic. Cholangio-hepatitis is an infection which is difficult to control; antibiotics should be reserved for acute exacerbations of fever. Sometimes the organisms responsible may be isolated by blood culture or culture of a liver biopsy, in which case sensitivity tests will indicate the appropriate antibiotic. If it is not possible to isolate the causative organism the recommendations given on page 572 should be followed.

Patients with biliary cirrhosis, like those with diffuse hepatic fibrosis and post-necrotic scarring, may require treatment for fluid retention, alimentary bleeding or encephalopathy. Jaundice tends to be severe and their main problem is usually pruritus. Antihistamine drugs (e.g. promethazine hydrochloride) may help to alleviate the pruritus. Alternatively methyltestosterone (25 mg sublingually) or norethandrolone (10 mg t.i.d.) can be used. These androgens, although sometimes helpful, may aggravate the jaundice and produce hirsutism. Another approach to this serious problem is the use of an oral ion-exchange resin, cholestyramine in a dose of 4-12 g daily. This compound exchanges chloride for bile acids and since it may bind drugs any other oral medication should be given one hour before the administration of cholestyramine. The mild steatorrhea already present may be aggravated by cholestyramine and necessitate a low fat diet. When necessary, the energy intake may be increased by the use of supplements of medium chain triglycerides which are not dependent on bile salts for their absorption.

If jaundice persists for months or years, fat-soluble vitamins should be given parenterally, as they may not be absorbed from the intestine. Monthly intramuscular injections of 10 mg vitamin K and 1·25-2·5 mg of vitamin D given every three months are usually adequate. A water-soluble form of vitamin A should be given by mouth. Calcium supplements are also essential and may be given in the form of skimmed milk and calcium effervescent tablets, four tablets three times a day.

In *primary biliary cirrhosis* there is some evidence to suggest that treatment with an immunosuppressant drug, such as azathioprine, may slow down the progress of the disease, especially if therapy is initiated in the early stages.

Other Diseases involving Hepatic Fibrosis

Haemochromatosis

(BRONZED DIABETES)

This is an uncommon disease which usually affects males over 45 years of age. There is dispute about its aetiology. In some families the condition appears to be inherited as an autosomal dominant with impaired penetrance (p. 7). When no genetic predisposition is evident there is often a history of excessive alcohol intake. For unknown reasons excessive absorption of iron occurs over many years. The deposition of this iron in the tissues appears to be responsible for most of the features of the condition. Pathologically, the findings include the distribution of iron-containing pigment (haemosiderin) throughout many organs in the body, but particularly the liver, heart and pancreas. Possibly as a result of direct mechanical destruction of parenchymal cells, diffuse hepatic fibrosis occurs.

Clinical Features. These include those of hepatic cirrhosis, diabetes mellitus and cardiac failure. A leaden-grey colour of the skin is characteristic, and is due to deposition of iron pigment and excess melanin. The diagnosis may be confirmed by a liver biopsy, in which iron can be demonstrated histochemically and by the finding of an elevated plasma iron level and complete or nearly complete saturation of the plasma iron binding capacity. Haemochromatosis must be distinguished from haemosiderosis which may result from repeated blood transfusions or from siderosis due to excessive administration of iron parenterally; iron overload induced in these ways is seldom accompanied by cell damage or fibrosis but this can occur from dietary overload (p. 128).

Treatment. This involves a combination of therapies for hepatic cirrhosis (p. 563) and for diabetes mellitus (p. 686). The body stores of iron should be reduced by repeated withdrawal of blood. Approximately 500 ml (which contains about 225 mg of iron) should be removed every one to two weeks until the plasma iron level falls to 100-150 micrograms/100 ml; this may take two years or more. Thereafter venesection should be done at suitable intervals in order to keep the plasma iron in the normal range.

Hepato-lenticular Degeneration

(WILSON'S DISEASE)

This is a very rare familial disease in which hepatic fibrosis appears to be secondary to the deposition of large amounts of copper in the liver parenchyma. The condition is described on page 876.

Syphilitic Cirrhosis

Congenital and acquired syphilis are rare causes of fibrosis of the liver. The former is associated with other stigmata of congenital syphilis, and the liver is enlarged as a result of intralobular and interlobular fibrosis. In acquired syphilis hepatic involvement is rare, but when it occurs the lesions present are usually gummata, which undergo fibrosis and scarring; the liver may be considerably enlarged.

Schistosomiasis (Bilharziasis)

Infection with *Schistosoma mansoni* or *japonicum* (p. 976) is an important factor in causing hepatic fibrosis in countries where bilharziasis is endemic. Malnutrition is usually present in these areas and probably contributes to the development of the fibrosis. The liver and spleen may be greatly enlarged.

Congenital Hepatic Fibrosis

This rare disorder is probably part of the visceral manifestations of polycystic disease (p. 617). The principal features are a large hard liver, splenomegaly, portal hypertension and abnormalities of the kidneys. Liver function is usually normal.

New Growths of the Liver

Primary Carcinoma of the Liver

This condition occurs mainly in males over middle age. Its incidence varies greatly in different parts of the world; it is a rare tumour in Britain but it is one of the most common forms of malignant disease in the South African Bantu. It usually occurs in association with hepatic cirrhosis. The tumour may be of liver cell or bile-duct type, and develops either as a large single nodule, sometimes almost completely occupying one lobe of the liver, or as a more diffuse form, with several nodules throughout the organ.

Symptoms and signs include vague gastrointestinal complaints, weakness, ascites, loss of weight, right upper quadrant pain and occasionally symptoms referable to metastatic deposits. Unexplained fever is a common feature, and if this occurs in a known case of hepatic cirrhosis and is associated with rapid development of ascites or marked loss of weight, hepatic carcinoma should be suspected. The detection of α-fetoprotein in the blood is diagnostic although it may be present in only 40 per cent of patients with hepatoma in Britain. Hepatic scintiscanning may reveal single or multiple filling defects.

Secondary Neoplasms of the Liver

These are relatively common, and are often secondary to primary carcinoma in the bronchus, breast, abdomen or pelvis. The metastatic foci may be multiple or single. Dissemination throughout the peritoneum frequently results in ascites.

Symptoms of the primary neoplasm are absent in about half the cases. Cirrhosis of the liver may be suspected from the hepatomegaly; the spleen, however, is rarely enlarged. There is usually a rapid enlargement of the liver, fever, weight loss and jaundice. Tests of liver function may show no impairment until late in the course of the disease. If ascites is present the fluid usually has a high protein content and may be blood-stained; cytological examination will often reveal malignant cells. Diagnosis may be made by needle biopsy of an enlarged area of the liver, laparotomy or radio-isotope scanning.

DISEASES OF THE GALL-BLADDER AND BILE DUCTS

Anatomy and Physiology

Bile, an aqueous solution of organic and inorganic solutes, has a complex and variable composition. It is formed by a conjunction of filtration, active transport and absorption. The major solutes are bile salts, phospholipids, cholesterol and bilirubin. The inorganic solutes are sodium, potassium, bicarbonate, calcium and magnesium. The relative proportions of the cations are similar to that of plasma. Following secretion by the hepatocyte into the biliary canaliculi bile flows down the bile duct system into the gall-bladder and duodenum. The function of this integrated system is to deliver bile to the gall-bladder where it is stored and concentrated prior to delivery into the duodenum at appropriate times to aid in the digestion and absorption of dietary lipids. Up to 2 litres of bile are secreted daily by the liver. Ten-fold concentration occurs in the gall-bladder as the result of the absorption of isotonic sodium chloride and bicarbonate.

After the ingestion of food the sphincter of Oddi relaxes, the gall-bladder contracts, and its contents are expelled through the cystic duct into the common bile duct and duodenum. The stimulus for this activity is the presence of food in the upper part of the small intestine, as a result of which cholecystokinin (pp. 431 and 488), is secreted into the blood by the mucosa of the duodenum and jejunum. This compound acts directly on the wall of the gall-bladder causing it to contract. Fats and foods rich in fat are especially effective in causing bile to be discharged by the gall-bladder. In addition, the gall-bladder and biliary sphincter appear to be reciprocally innervated: vagal stimulation results in contraction of the gall-bladder with relaxation of the sphincter, while stimulation of the sympathetic nerves produces the reverse effects.

The sympathetic nerves to the gall-bladder are connected, through the coeliac plexus, with the lower six thoracic segments in the spinal cord. This fact probably explains the referred pain, tenderness and hyperaesthesia over the area of somatic distribution of the lower thoracic nerves posteriorly which is frequently found in gall-bladder disease. The pain in the shoulder which is more rarely present in biliary disease is probably due to direct irritation of a branch of the phrenic nerve below the diaphragm.

Evaluation of Gall-bladder Structure and Function

The estimation of the concentrating power of the gall-bladder and of its ability to contract, and an assessment of the patency and configuration of the bile ducts are an essential part of the investigation of patients suspected of having gall-bladder disease.

1. **Radiography of the Abdomen.** A plain film of the abdomen may demonstrate the presence of stones in the gall-bladder or ducts, the soft tissue mass of an inflamed gall-bladder, gas in the biliary tract (e.g. from a fistula between the gall-bladder and intestine) or calcification in the pancreas. About 30 per cent of gall-stones are radio-opaque; they are often laminated and bear a constant relationship to the liver margin.

2. **Cholecystography** is the most useful single procedure in the diagnosis of gall-bladder disease. An organic iodine-containing compound (e.g. Telepaque) is taken by mouth on the evening before the examination. The compound is absorbed, secreted by the liver in the bile and concentrated in the normal gall-bladder. Under these circumstances, a shadow is seen in the area of the gall-bladder on radiological examination the following morning; failure to visualise the gall-bladder usually indicates gall-bladder disease or obstruction in the cystic duct (non-functioning gall-bladder). If the gall-bladder is functioning sufficiently to produce a shadow, any non-opaque stones will probably be demonstrated. Rarely, tumours of the gall-bladder may also be seen.

3. **Cholangiography.** INTRAVENOUS CHOLANGIOGRAPHY. Biligrafin (iodipamide methylglucamine) is a substance which is concentrated and excreted by the liver. In subjects with reasonably normal liver function and with the plasma bilirubin concentration less than 2 mg 100 ml, intravenous administration of the dye permits visualisation of the main biliary ducts as well as the gall-bladder. It is a most valuable investigation when the gall-bladder has been found to be non-functioning on oral cholecystography. In the cholecystectomised patient it is the only method of demonstrating the bile ducts and the presence of a stone, and it is valuable in showing the existence of intrahepatic stones or other pathology.

OPERATIVE AND POST-OPERATIVE CHOLANGIOGRAPHY. In operations on the biliary tract the patency of the ducts may be demonstrated by the injection of the non-irritant radio-opaque substance, diodone, into the extrahepatic ducts. A similar procedure should be used post-operatively before withdrawing a drainage tube which has been inserted into the common bile duct.

PERCUTANEOUS TRANSHEPATIC CHOLANGIOGRAPHY. This is of value in the patient with obstructive jaundice, in whom i.v. cholangiography is not possible and for whom surgery has been decided. On the morning of the planned operation a catheter is introduced directly into the liver parenchyma under local anaesthetic. Where there is an extrahepatic obstruction a dilated intrahepatic duct is readily punctured and following aspiration of bile, radio-opaque contrast is injected under fluoroscopic control. This technique provides the surgeon with accurate information regarding the site and often the nature of the obstruction. It is carried out immediately prior to surgery because of the risk of biliary leakage and peritonitis.

CHOLEDOCHOPANCREATOGRAPHY. Retrograde cannulation of the common bile duct and pancreatic duct via the ampulla of Vater is now feasible as the result of the availability of the flexible fibreoptic duodenoscopes. This technique permits retrograde definition of these duct systems and thereby further increases the accuracy of diagnosis of biliary tract disease.

Acute Cholecystitis

Aetiology and Pathogenesis. Acute cholecystitis is rarely due primarily to infection of the gall-bladder, but almost always occurs in association with obstruction to the cystic duct or neck of the gall-bladder, upon which infection is usually superimposed. By far the most common cause of obstruction is gall-stones but inspissated bile, oedema of the duct, or more rarely enlarged lymph nodes or tumour may produce the same effects. The gall-bladder swells as a result of the accumulation of inflammatory exudate and mucin and of the obstruction, which prevents evacuation of bile. In consequence, its vascular supply is compressed and necrosis and perforation may follow. The most common infecting organisms are *Strep. faecalis* and *Strep. viridans*, and *Esch. coli*. Whether the infecting organisms reach the gall-bladder via the bile ducts, the lymphatics or the blood stream is uncertain. It is possible that cholecystitis may sometimes be initiated by the chemical irritation of bile salts, when the latter reach abnormally high concentration in the gall-bladder; this could occur either when the outlet to the organ is obstructed and absorption of water and inorganic salts continues, or from an increase in the concentration of the bile acids secreted by the liver.

Acute bacterial cholecystitis can occur without obstruction in the course of typhoid or paratyphoid fever. It may also rarely develop in the septicaemic stage of other infective processes, without obstruction to the cystic duct.

Pathology. The organ may show any degree of change from slight congestion to gross inflammation, swelling and tenseness. In the latter case, ulceration of the wall may be present. Occasionally, the gall-bladder may be full of pus (empyema) and this is usually associated with complete blockage of the cystic duct by a stone.

Clinical Features. Although the disease can occur at any age, patients are most commonly women who have borne several children and are aged between 40 and 60 years. Obesity is often present.

When there is no obstruction in the cystic or common bile duct, the patient is nauseated, complains of discomfort in the upper abdomen and is febrile. On examination, tenderness is maximal in the right hypochondrium when the patient takes a deep breath. When obstruction occurs, as it does in the majority, the patient develops a sudden severe pain due to biliary colic (p. 573), and becomes restless. Jaundice is in most cases absent or slight, and if present suggests obstruction (stone or oedema) in the common bile duct, or ascending cholangitis and cholangiohepatitis. A history of previous attacks of abdominal pain is commonly obtained.

Laboratory Data. Polymorphonuclear leucocytosis is usual. Cholecystography often fails to define the gall-bladder and intravenous cholangiography may also be unsuccessful because of mild hepatic dysfunction. However, a plain radiograph of the upper abdomen may be helpful by showing radio-opaque stones.

Course and Prognosis. In the majority of cases of acute cholecystitis, the symptoms subside in a few days with conservative therapy, though a recurrence of the attack after weeks, months or years is common. In a few cases, however, serious complications occur, which, if left untreated, can be fatal. In severe infections with complete obstruction, the gall-bladder becomes acutely tender, and muscular rigidity spreads. Empyema of the gall-bladder may develop in a few hours, and perforation with localised or rarely generalised peritonitis can follow. Subphrenic abscess, acute pancreatitis, or ascending cholangitis and cholangiohepatitis may also result. When such complications develop the patient is clearly seriously ill, with high fever and rapid pulse.

Differential Diagnosis must be made from other causes of severe upper abdominal pain. These include appendicitis, perforation of a peptic ulcer, myocardial infarction, renal colic, acute pyelonephritis, intestinal colic, herpes zoster, pleurisy, acute pancreatitis, epidemic myalgia (Bornholm disease) and acute porphyria.

Treatment. Initial management is conservative and surgical intervention in the acute stage of the disease is indicated only when signs and symptoms occur which suggest the development of empyema of the gall-bladder. Usually simple drainage of the gall-bladder with removal of the contained stones is then carried out, cholecystectomy being performed a few weeks later when the acute phase has subsided.

The majority of patients will recover with conservative treatment. In the acute stages, medical therapy consists of maintaining salt and water balance, and the relief of pain by the measures described for the treatment of biliary colic (p. 575). If, as is usual, the bacteria responsible for the infection cannot be isolated, ampicillin or colomycin are the drugs of first choice. Surgical removal of the gall-bladder is usually advised after the acute symptoms have subsided, especially if gall-stones are present. Some surgeons practise cholecystectomy when the diagnosis of acute cholecystitis is made; operation at this time, however, may be more hazardous.

Chronic Cholecystitis

The term 'chronic cholecystitis' is used to denote chronic disease of the gall-bladder whether due to calculi, to infection or to the deposition of cholesterol.

Cholelithiasis (Gall-stones) and Chronic Calculous Cholecystitis

Gall-stones (cholelithiasis) occur in 5 to 10 per cent of the population and are found about five times more commonly in females; their incidence increases with age. In a few cases no evidence of cholecystitis is found, but in the majority cholelithiasis is associated with chronic inflammation of the gall-bladder of varying degree. The wall may be greatly thickened and fibrosed, and the organ is frequently shrunken. The destruction of mucosa leads to impairment in concentrating power.

Aetiology of Gall-stones. The detailed mechanism of gall-stone formation is not fully understood but evidence is accumulating that changes in the physico-chemical properties of bile are the main determinants.

Cholesterol is the principal component of most gall-stones and its precipitation from bile is highly relevant. Cholesterol solubility is determined by the ratio of cholesterol to bile acids and phospholipids and the most important chemical change in the bile of patients with gall-stones is an excess of cholesterol in relation to bile acids and phospholipids. Such changes in its composition precede the development of calculi and can be demonstrated in bile both from the liver and from the gall-bladder. Thus the liver and not the gall-bladder is the source of the abnormal bile. It appears that the size of the bile salt pool is diminished, and that this is associated with a reduced secretion of bile salts. This in turn diminishes the phospholipid content of bile and results in lithogenic bile supersaturated with cholesterol. The gall-bladder plays a vital role in providing stasis and sites for the formation of stones, a process further enhanced if infection ensues.

Classification of Gall-stones. There are three main types of gall-stones:

(1) *Cholesterol Stones.* These are composed almost entirely of cholesterol and are frequently called 'metabolic stones'. They occur singly or in pairs in most cases.

(2) *Pigment Stones.* These stones, which are always numerous, are composed almost entirely of bile pigment. They occur in association with haemolytic diseases and presumably result from the excessive excretion of bilirubin by the liver. They are rare.

(3) *Mixed Stones.* These are the most common type of stone; they are usually present in large numbers and consist of lamellated layers of cholesterol, calcium and bilirubin.

Clinical Features. Patients are most commonly obese women of middle age. The nature and severity of their complaints depend upon the position of the stones in the biliary tract and upon the degree of associated infection. If the stones remain in the gall-bladder, there may be no symptoms.

BILIARY COLIC. This is the cardinal symptom of chronic calculous cholecystitis. It occurs when a stone lodges in the cystic or common bile duct, and it is frequently the first and only clinical evidence of the presence of gall-stones. The attack may be precipitated by dietary indiscretion or undue physical effort, or it may occur without apparent reason. A sudden pain is felt in the epigastrium, and this gradually increases with slight wave-like exacerbations, and usually moves to the right hypochondrium. The pain, which is frequently agonising, may then be referred, as in acute cholecystitis, to the right side and back, or to the right shoulder. Vomiting and nausea frequently occur. The pain lasts several hours, and then subsides, often suddenly, leaving a feeling of soreness which persists for some days. During the attack the patient is restless, tenderness and muscle spasm in the right upper quadrant of the abdomen are found and, if the stone remains in the cystic duct, acute cholecystitis may develop. Jaundice appears in a little over half of the patients in whom the stone lodges in the common bile duct, and its occurrence is dependent upon the degree of blockage of the duct. The jaundice may be slight or latent and revealed only by plasma bilirubin determination. Commonly in such cases, however, bile may appear transiently in the urine, or the patient may give a history of having noted a temporary darkening of the urine or lightening of the colour of the stool. In other cases, frank obstructive jaundice develops simultaneously with episodes of biliary colic. The obstruction is not usually complete, and often lasts for little more than one to two weeks. In some of these cases the symptoms and signs of cholangitis and cholangio-hepatitis develop: fever and rigors occur, and the liver may enlarge.

'GALL-BLADDER DYSPEPSIA.' A proportion of patients with chronic calculous cholecystitis complain of chronic flatulent dyspepsia definitely related to meals and frequently precipitated by fatty or fried foods. Most patients describe this as discomfort in the epigastrium and a feeling of fullness and nausea. Constipation with transient attacks of diarrhoea may be present. This symptom complex has been called 'gall-bladder dyspepsia', and organic disease of the gall-bladder or the presence of gall-stones has been held responsible for its production. Since, however, many patients with organic disease of the gall-bladder never complain of dyspepsia, and since similar clinical features occur in association with other organic and functional conditions of the gastrointestinal tract, such dyspepsia should be attributed to gall-bladder disease only when other causes have been carefully excluded.

Laboratory and Radiological Data. The urine may or may not contain bilirubin, depending upon the presence of obstruction to the common bile duct. After the subsidence of an acute attack of colic, radiological examination of the abdomen should be carried out and cholecystography should be performed. By these means stones and/or a poorly functioning gall-bladder will usually be demonstrated.

Differential Diagnosis. In the absence of biliary colic and obstructive jaundice, the diagnosis of chronic calculous cholecystitis presents considerable difficulty. Other conditions associated with dyspepsia, e.g. hiatus hernia, peptic ulcer, carcinoma of the stomach, chronic gastritis and chronic pancreatitis, have to be excluded by appropriate methods. It is a sound rule not to diagnose organic disease of the gall-bladder from the presence of dyspepsia alone without the radiological demonstration of gall-stones or an abnormal cholecystogram.

In the differentiation of biliary pain due to cholelithiasis from other conditions producing acute abdominal pain (p. 500) it is helpful to note that it occurs in discrete episodes of usually less than a day and separated by symptom-free periods of weeks or months. Cholecystography is again necessary to confirm the origin of the symptoms and signs. It should also be appreciated that patients with organic disease of the biliary tract not infrequently have disorders elsewhere in the alimentary tract, in particular hiatus hernia and diverticular disease of the colon. Symptoms arising from these conditions must be carefully assessed before advising cholecystectomy.

When obstructive jaundice is present differential diagnosis rests between stone in the common bile duct and carcinoma of the head of the pancreas or of the biliary tract. Loss of weight may be marked in the latter condition and biliary colic is absent, while the jaundice is usually progressive and without fluctuation. Fever is also usually absent in carcinoma, at least in the early stages. The palpation of a smooth, tender, distended gall-bladder favours obstruction of the common bile duct by neoplasm rather than stone, since a gall-bladder which is the seat of chronic inflammation and gall-stones is usually incapable of distension. The differential diagnosis between obstruction of the common bile duct by a neoplasm and obstruction due to a 'silent' stone, i.e. a stone impacted in the duct which does not produce the symptoms of biliary colic, is especially difficult. Such 'silent' common duct stones may be found at operation in patients in whom neoplasm was suspected pre-operatively.

Treatment. There is no satisfactory treatment for chronic calculous cholecystitis other than surgical removal of the gall-bladder and any stones that may be in the biliary tract. Operation, however, should not be undertaken for the presence of stones *per se*, but advised for patients who have suffered one or more attacks of biliary colic or episodes of acute cholecystitis, or in whom jaundice and evidence of cholangitis are present and have persisted for a period of some weeks. Operation is strongly contraindicated for symptoms of 'gall-bladder dyspepsia' in the absence of additional evidence of organic gall-bladder disease. It should be avoided if possible in patients who are poor surgical risks because of cardiovascular, pulmonary or renal disease. Pre-operative weight reduction is necessary for the obese.

Medical management of chronic calculous cholecystitis includes the treatment of the acute attack of biliary colic, the treatment of infection in the gall-bladder and biliary tract and the treatment of dyspepsia and obesity.

Biliary Colic. Although morphine sulphate is known to cause contraction of the biliary sphincter, it remains one of the most effective drugs for the relief of biliary colic, provided it is given in large enough doses, i.e. 15-20 mg subcutaneously and repeated in one hour if relief is not obtained. Concomitantly, an intramuscular injection of propantheline bromide (30 mg) may be given to relieve spasm. In less severe cases pethidine, 100 mg by intramuscular injection, may be satisfactory, and may be repeated in two hours.

Infection in the Biliary Tract. Antibiotics and chemotherapeutic agents should be used when fever is present, i.e. either in acute cholecystitis or in acute cholangitis and cholangio-hepatitis developing in the course of chronic calculous cholecystitis. Their use in these conditions is described on page 572.

Diet. The value of dietetic treatment in patients in whom cholecystectomy is contraindicated remains debatable. Foods which precipitate or aggravate symptoms should be avoided. Since biliary stasis is believed to predispose to the formation of gall-stones a moderate intake of fats is permitted. This promotes drainage of the biliary system.

Dissolution of Gall-stones. Evidence is now available that the oral feeding of a bile acid (chenodeoxycholic acid) to patients with gall-stones leads to diminution in size and ultimate dissolution of cholesterol stones as a result of the increase in the solubility of the bile. Tests are currently under way to determine whether stone formation can be prevented by long-term administration of chenodeoxycholic acid to patients with lithogenic bile. The value of this form of therapy and its possible complications are yet to be determined.

Chronic Non-calculous Cholecystitis

This is a very rare cause of symptoms referable to the gall-bladder. Infection of the gall-bladder is probably secondary to mechanical or chemical factors. Partial obstruction of the cystic duct by inflammatory swelling can result in a chronic inflammation of the wall of the gall-bladder.

Clinical Features are the same as those associated with calculous cholecystitis but are usually milder. Biliary colic and mild jaundice can also occur, the latter being due to ascending cholangitis.

Diagnosis of chronic cholecystitis without stones depends upon the clinical features and the objective findings of gall-bladder disease as revealed by cholecystography, namely the presence of a gall-bladder which fails to function normally and in which gall-stones cannot be demonstrated.

Treatment of the confirmed case of non-calculous cholecystitis is similar to that described under calculous cholecystitis (p. 574), except that medical treatment may be given a longer trial before resorting to surgery. In those cases in which operation is not advisable, medical therapy directed to eliminate biliary stasis and increase bile flow can be more vigorous than in calculous cholecystitis, since the danger of a stone becoming impacted in the common bile duct is absent. Magnesium sulphate taken before breakfast and olive oil before lunch and the oral administration of bile salts have a more important place in treatment.

Cholesterolosis of the Gall-bladder

This condition may occasionally be found at operation in patients diagnosed as suffering from chronic calculous cholecystitis. The mucosa of the gall-bladder is red and studded with deposits of cholesterol and other lipid material; cholesterol calculi may be present. The mechanism of the cholesterol deposition is not yet fully understood though infection is not believed to play a part. Autopsy studies show that cholesterolosis can exist without symptoms. The patients are predominantly obese females; symptoms, when present, are due to associated cholelithiasis or calcification of the gall-bladder wall (porcelain gall-bladder). The presence of cholesterolosis is not usually suspected, and is revealed only at operation. Cholecystography usually shows impairment of gall-bladder concentrating power, and cholesterol crystals may be seen in large numbers in the fluid obtained by duodenal aspiration. Treatment is similar to that for chronic calculous cholecystitis.

Biliary Dyskinesia

Biliary dyskinesia has been defined as an obstruction to bile flow into the duodenum due to a neuromuscular disturbance of the biliary sphincter, as a result of which symptoms suggestive of organic disease of the gall-bladder are present. Its existence is disputed by many authorities. It is extremely rare to find a patient with vague fat-intolerant dyspepsia and mild biliary colic attributed to the disorder, in whom there are not present other more definite mechanisms such as hiatus hernia, pancreatitis, ulceration of the second part of the duodenum, an inflamed diverticulum in relation to the ampulla of Vater. The failure of sphincterotomy to give relief to all but a few substantiates this impression. In suspect cases a trial of antispasmodic drugs, e.g. propantheline bromide 15 mg given every four hours or glyceryl trinitrate 0·5 mg as required is justified.

Tumours of the Gall-bladder and Bile Ducts

Primary Carcinoma of the Gall-bladder

This disease is not common; it occurs in less than 4 per cent of patients with cholelithiasis.

Clinical Features. Most patients are elderly women who give a history of calculous cholecystitis for many years. Frequently the symptoms do not differ from those of chronic cholecystitis, diagnosis being made at operation. Pain in the epigastrium and right upper quadrant of the abdomen gradually becomes constant and severe. A mass can be felt in the gall-bladder area in about 50 per cent of cases. Complete obstructive jaundice, from compression or invasion of the common bile duct, is common and persists without remission. Fever, loss of weight and vomiting are usual in the late stages. The occult blood test of the faeces is frequently negative.

Diagnosis is usually made at operation undertaken for obstructive jaundice, suspected to be due to stone in the common bile duct or carcinoma of the head of the pancreas.

Treatment. The majority are inoperable. Occasionally the tumour is confined to the gall-bladder or has extended only slightly into the liver. In these circumstances cholecystectomy and occasionally local or partial hepatectomy is possible.

Primary Malignant Tumours of the Extrahepatic Biliary Ducts

Tumours of these ducts are rare. An insidious onset of jaundice is almost invariable, and eventually the features are those of complete obstructive jaundice. Pain is common and may be similar to that of biliary colic; the features of superimposed cholangio-hepatitis often develop. The occult blood test of the faeces is usually positive. Operative removal of the tumour is rarely possible.

Benign Tumours

Papillomas of the gall-bladder or bile ducts are rare but in the latter situation may give rise to obstructive jaundice.

PREVENTION OF DISEASES OF THE LIVER AND BILIARY TRACT

Acute Parenchymal Disease of the Liver. The hazards from exposure to toxic agents used in industry, e.g. carbon tetrachloride, phosphorus and others, have been greatly reduced in recent years by appropriate measures enforced by Acts of Parliament. Acute hepatic disease may occasionally result from the therapeutic use of gold or arsenic. During treatment by these drugs careful watch should be kept for signs which suggest liver damage; if these appear the administration of the drug should be stopped immediately. It is obvious that hepatotoxic drugs should not be used in patients already suffering from chronic parenchymal liver disease. A number of organic chemicals may cause damage to the liver, including such drugs as chlorpromazine and also oral contraceptive agents. The Medicines Commission has been set up in Britain to safeguard patients from this form of iatrogenic disease and to encourage surveillance and care in the use of all new drugs.

Chronic Parenchymal Disease of the Liver and Disease of the Biliary Tract. Prevention of chronic disease of the liver consists partly of preventing the occurrence of acute hepatic disease (p. 548). This is particularly true in the case of post-necrotic scarring and post-infective cirrhosis. The high incidence of cirrhosis of the liver in tropical countries in which the dietary intake of first-class protein and essential food factors is deficient could undoubtedly be reduced by the provision of a more satisfactory diet. Such a diet can be made available only if there develops greater co-operation on the part of economists, agriculturalists and statesmen of many countries than exists today. Diffuse hepatic fibrosis occurring as a sequel to fat infiltration may occur where there is a large disparity between the intake of calories and of essential food factors. This was formerly seen commonly among chronic alcoholics. The reduction in the consumption of alcohol, advances in education and improved living standards have all contributed to a decline in the number of cases of alcoholic cirrhosis in Britain.

Progressive deterioration of liver function can be prevented in haemochromatosis by regular venesection in the early stages and in hepatolenticular degeneration by penicillamine; moreover the genetic nature of these two rare diseases makes it possible to anticipate their development and to take the necessary prophylactic measures.

Biliary cirrhosis can be prevented by prompt surgical relief of biliary obstruction and treatment of any associated infection. A moderate intake of neutral fat, with the avoidance of sedentary habits, helps to prevent biliary stasis, which is a potent factor in stone formation. The association of gall-bladder disease and cholelithiasis with obesity provides additional justification if any more is needed for the prescription of an anti-obesity diet as a preventive measure in persons who are overweight.

J. P. A. McManus.
John Richmond.
J. S. Robson.

Further reading:

Popper, H. & Schaffner, F. (1965). *Progress in Liver Diseases*, vol. 2. London: Heinemann.

Popper, H. & Schaffner, F. (1970). *Progress in Liver Diseases*, vol. 3. London: Heinemann.

Sherlock, S. (1968). *Diseases of the Liver and Biliary System*, 4th ed. Oxford: Blackwell.

Smith, R. & Sherlock, S. (1964). *Surgery of the Gall-bladder and Bile Ducts*. London: Butterworth.

Zuckerman, A. J. (1970). *Virus Diseases of the Liver*. London: Butterworth.

Diseases of the Kidney and Urinary System

STRUCTURE AND MODE OF ACTION OF THE KIDNEYS

THE kidneys are each composed of approximately one million nephrons, the basic structure of one of which is illustrated in Figure 77.

The blood supply of the kidney is relatively large and amounts to about one-quarter of the cardiac output at rest, i.e. 1,300 ml per minute. The afferent arterioles which give rise to the glomerular capillaries arise from branches of the renal artery. Emerging from the glomeruli the capillaries unite to form the efferent arterioles which then supply blood to the proximal and distal convoluted tubules surrounding the glomeruli. The medullary region of the kidney is supplied by arterioles which arise from those glomeruli situated in the deeper regions of the cortex.

For a short distance the efferent arterioles and distal convoluted tubules are in contact, and at this point the tubular cells become tall and columnar in character, forming the macula densa. The wall of the arteriole is thickened by cells which contain large secretory granules. These structures together constitute the juxtaglomerular apparatus which is intimately concerned in the regulation of the volume of the extracellular fluids and blood pressure.

The hydrostatic pressure within the glomerular capillaries of about 70 mm Hg results in the filtration of fluid from the plasma into Bowman's capsule. This fluid is identical in its composition with plasma except that it normally contains no fat and very little protein. The filtrate thus formed then flows through the various parts of the tubule and is modified according to the needs of the body by tubular secretion and by the selective reabsorption of its constituents.

THE FUNCTIONS OF THE KIDNEYS

In health the volume and composition of the body fluids vary within narrow limits. The kidneys are largely responsible for maintaining this constancy and the excretion of the waste products of metabolism represents merely one aspect of this task. The various renal functions are conveniently considered under the following headings and some are shown diagrammatically in Figure 77.

1. **Regulation of the Water Content of the Body.** About seven-eighths of the water filtered by the glomerulus is reabsorbed by the proximal tubules. The remaining water passes through the distal tubules and collecting ducts where its reabsorption is influenced chiefly by vasopressin, the antidiuretic hormone of the posterior pituitary. In the presence of vasopressin the collecting ducts become permeable to water which is then passively reabsorbed in response to the high concentration of sodium chloride and urea which exists in the medullary interstitium. The urine then becomes concentrated. In the absence of vasopressin the collecting ducts are impermeable to water. In these circumstances a dilute urine is formed by the tubular reabsorption of sodium without water. Disorders

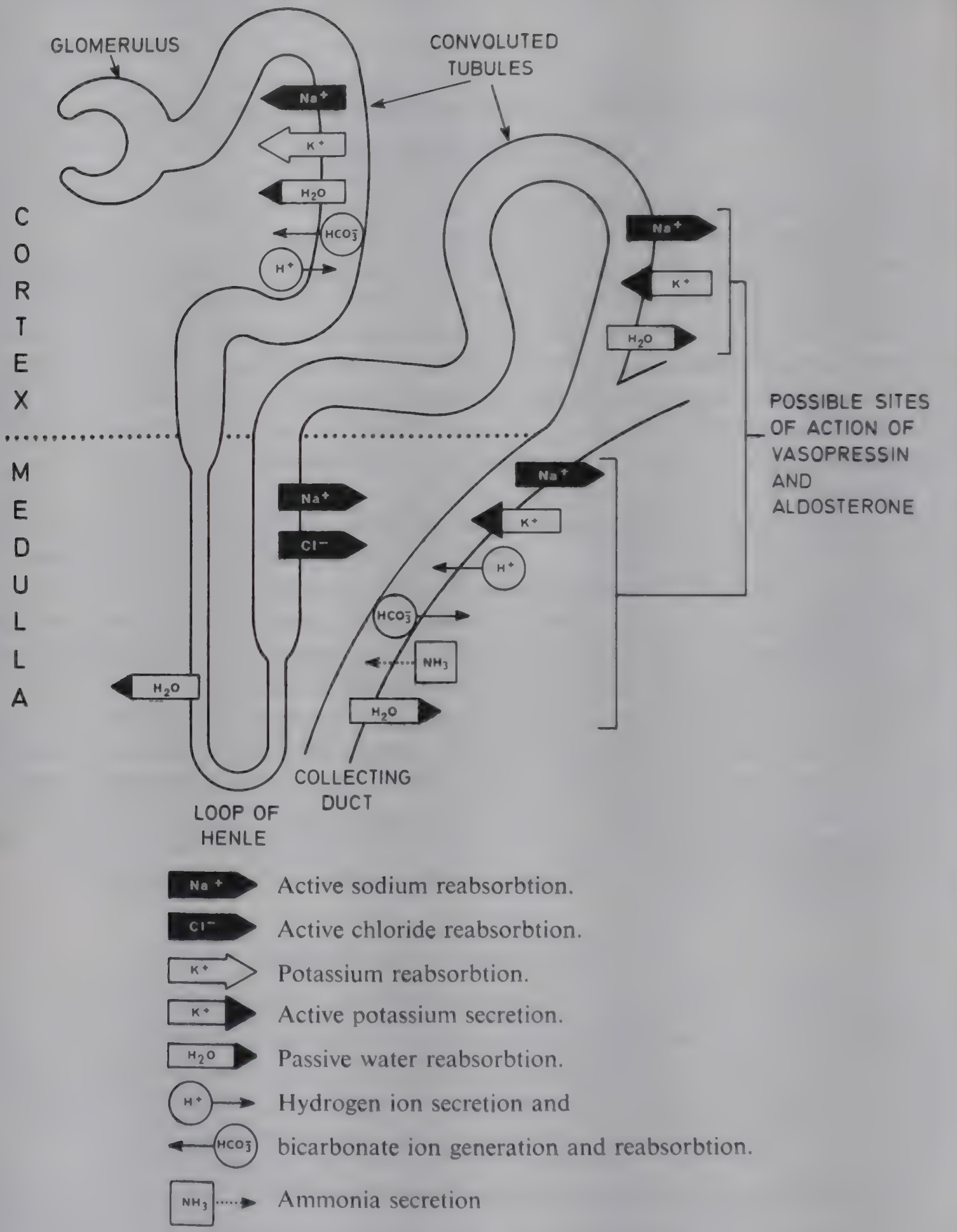

GLOMERULUS
CONVOLUTED TUBULES
CORTEX
MEDULLA
Na^+
K^+
H_2O
HCO_3^-
H^+
Cl^-
NH_3
POSSIBLE SITES OF ACTION OF VASOPRESSIN AND ALDOSTERONE
LOOP OF HENLE
COLLECTING DUCT
Na^+ Active sodium reabsorbtion.
Cl^- Active chloride reabsorbtion.
K^+ Potassium reabsorbtion.
K^+ Active potassium secretion.
H_2O Passive water reabsorbtion.
H^+ Hydrogen ion secretion and
HCO_3^- bicarbonate ion generation and reabsorbtion.
NH_3 Ammonia secretion

FIG. 77

Arrangements of some of the events concerned in urine formation. In the proximal tubule about seven-eighths of the filtered sodium, potassium and water are reabsorbed. The greater part of the filtered bicarbonate is also reabsorbed here by a process which involves the secretion of hydrogen ions. The sodium and chloride reabsorbed in the ascending limb of the loop of Henle is largely responsible for the hyperosmolality of the medullary interstitium. In the distal tubule and collecting duct potassium is passively secreted in response to the negative PD created by active sodium reabsorption. Hydrogen and ammonium ions are also secreted there and water is passively reabsorbed in the presence of vasopressin.

of the water-regulating mechanism which result in oliguria or polyuria are described on pages 583 and 584.

2. **Regulation of the Electrolyte Content of the Body.** The electrolyte content of the body is kept remarkably constant as a result of selective reabsorption by the renal tubules. A large part of the filtered sodium and probably all the potassium are actively reabsorbed in the proximal convoluted tubules. The remainder of the sodium passes into the distal tubule and collecting ducts where its reabsorption appears to be under the influence of hormones of the adrenal cortex, especially aldosterone. With reduced secretion of these hormones, excessive quantities of sodium and chloride ions are lost in the urine, whereas with the administration of corticosteroids, sodium retention occurs. The reabsorption of sodium in the distal parts of the nephron creates a negative intraluminal potential with respect to the peritubular fluid; this encourages passive secretion of potassium into the tubule.

The dual actions of the adrenocortical hormones and of the antidiuretic hormone on the renal tubules play an important role in determining the total volume of water and the electrolyte content of the body. The rate of secretion of vasopressin is mainly determined by changes in osmolality of the blood; aldosterone secretion is influenced *inter alia* by changes in the pulse pressure within the internal carotid artery and in the renal artery; this influences the rate of secretion of renin by the juxtaglomerular apparatus. It has also been shown that proximal tubular reabsorption of water and salt is influenced by the volume of the blood and the extracellular fluid. How this control is mediated is unknown but the activity of a third so-called natriuretic hormone has been postulated.

3. **Maintenance of the Normal Acid-base Equilibrium of the Blood.** The ingestion and oxidation of a normal diet results in the formation of substances which yield hydrogen ions in aqueous solution. Carbonic acid is eliminated by the lungs as carbon dioxide but the other acids which include acetoacetic acid and the oxidative products of sulphur-containing proteins require the collaboration of an elaborate mechanism within the kidney for their disposal. These inorganic and organic acids are in the first instance partly neutralised by the blood and other buffer systems as described on pages 198 to 200. By itself this process leaves the blood abnormal in three respects, i.e. the hydrogen ion concentration remains increased above normal, the concentration of bicarbonate is reduced and the anions of the acids still require to be excreted. These abnormalities are corrected as follows:

1. Carbonic acid is generated within the renal tubular cells from CO_2 and H_2O under the influence of carbonic anhydrase. The hydrogen ions of this acid are secreted into the tubular lumen in exchange for filtered sodium which is then reabsorbed into the blood.

The bicarbonate ions liberated from the carbonic acid made in the renal tubular cells are absorbed with the sodium into the blood; this restores the concentration of plasma bicarbonate to normal and also regenerates other buffers in the body which have been titrated by the invading acids.

2. Some of the hydrogen ions are buffered in the urine by disodium hydrogen

phosphate to form dihydrogen sodium phosphate and in the distal tubules by ammonia to form ammonium ions. The anions of the inorganic and organic acids are then excreted in the urine largely as ammonium salts.

The degree to which these mechanisms operate is adjusted in accordance with the nature of the food ingested and the amount of endogenous acid production. In health, on a normal diet, 40-80 mEq of acid are excreted daily into the urine. When a diet consisting mainly of fruit and vegetables is taken alkaline sodium phosphate and bicarbonate are excreted in the urine and tubular secretion of hydrogen and ammonium ions is suppressed.

In disease states in which abnormally large amounts of organic acids are being formed, e.g. β-hydroxybutyric acid and acetoacetic acid in diabetic ketoacidosis, these processes are fully active and may be overwhelmed. Excess acid is retained in the blood and acidosis occurs. When renal tubular activity itself is severely affected by kidney disease these regulatory mechanisms fail and acidosis of renal origin develops.

4. **Retention of other Substances vital to Body Economy, e.g. Glucose, Amino Acids, Phosphate, Bicarbonate, Proteins.** Glucose is normally reabsorbed so completely by the proximal tubules that none can be detected in the urine by clinical tests. Renal glycosuria (p. 684) is a genetically determined benign defect of tubular reabsorption in which glucose appears in the urine in the presence of normal blood levels. More rarely other congenital or acquired abnormalities of tubular transport result in abnormal loss in the urine of amino acids, phosphate, sodium, potassium, calcium and water. These defects may occur singly or in combination. Examples of these disorders are cystinuria, familial hypophosphataemia, nephrogenic diabetes insipidus and the Fanconi syndrome, a disease chiefly of infancy and childhood.

In health the great bulk of the bicarbonate filtered by the glomeruli is removed from the urine by tubular reabsorption, and this becomes complete when the urine is acid. Idiopathic renal tubular acidosis is a rare congenital disease in which there is a defect in the power to reabsorb bicarbonate or to acidify the urine which then usually contains significant amounts of bicarbonate in the face of systemic acidosis. A similar tubular defect is commonly acquired as a result of renal disease such as pyelonephritis. Both types are apt to lead to osteomalacia (p. 142) and tissue calcification, especially in the kidneys, and to hypokalaemia.

In health only a small amount of protein (2 mg/100 ml) reaches the fluid in Bowman's capsule. The volume of glomerular filtrate, however, is so great that if this small amount were not reabsorbed, more than 3 g of protein rather than the normal 50 mg would be excreted in the urine in 24 hours.

5. **Excretion of Waste Metabolic Products, Toxic Substances and Drugs.** The end-products of metabolism, especially those of protein, include urea, uric acid, creatinine, phosphates and sulphates.

6. **Hormonal Functions.** The juxtaglomerular apparatus within the kidneys is believed to secrete renin, which is converted in the blood to angiotensin II. This substance increases the rate of aldosterone secretion by the adrenal cortex

and also causes vasoconstriction. This may be the sequence of events by which renal ischaemia produces hypertension. The kidney is the main source of erythropoietin necessary for normal erythropoiesis (p. 713). Prostaglandins are also present in renal tissue but their function there is unknown.

DIAGNOSIS OF RENAL DISEASE

In the majority of patients suffering from renal disease, symptoms and signs are not usually referred to the anatomical site of the kidneys. This is due to the fact that clinical features of renal disease most frequently arise from abnormalities in the chemical composition of the body or from hypertension. Their true origin therefore may be suspected only after the detection of urinary abnormalities, and the importance of a routine examination of the urine in clinical practice cannot be over-emphasised. The examinations which may be of value include the determination of the volume of urine passed in 24 hours, the presence of abnormal urinary constituents and bacteriological examination. Under certain standardised conditions the determination of the specific gravity and pH of urine is of value. In addition it may be necessary to obtain further information by some or all of the following investigations:

1. Chemical analysis of the blood and urine.
2. Tests of glomerular and tubular function.
3. Radiological examination of the abdomen, intravenous pyelography, cystoscopy, ureteric catheterisation with collection of urine samples from each kidney, retrograde pyelography, renal angiography, isotope renography and renal biopsy.

Urinary Volume

In health and in temperate climates the volume of urine excreted usually lies within the range of 800-2,500 ml per 24 hours. There is a limit to the power of the kidneys to concentrate urine and on a normal diet a minimum volume of 800 ml is required to excrete the solid urinary constituents which consist mainly of urea and electrolytes. Less solute has to be excreted when a diet rich in carbohydrate and fat and low in protein and salt is eaten, and as little as 250 ml of urine per 24 hours is sufficient in these circumstances.

Oliguria is the production of insufficient urine to enable solute to be excreted in adequate amounts and the *milieu intérieur* of the body to be preserved. If the concentrating power of the kidneys is seriously reduced or if the solute to be excreted in the urine is increased above the normal, as occurs, for example, in severe infections, a daily output of as much as 2-3 litres of urine may even be insufficient. Oliguria develops in conditions associated with a reduction in renal blood flow and rate of glomerular filtration, e.g. diseases giving rise to water and salt depletion, hypotension, cardiac failure, acute glomerulonephritis, and other parenchymal diseases of the kidneys. In these circumstances urine flow sometimes ceases completely and *anuria* develops. Anuria from this cause should be distinguished from urinary retention. In the latter case distension of the bladder will be found on examination of the abdomen, confirmed if necessary by catheterisation.

Polyuria denotes a persistent increase in urinary output. It must be distinguished from frequency of micturition, which may be defined as the frequent passage of small quantities of urine without an increase in the total volume.

There are two basic mechanisms which give rise to polyuria. It may be due either to the excretion of an abnormally large amount of solute so that elimination of an increased volume of water is required, or to a reduction in the ability of the kidney to concentrate urine and conserve water. The latter defect may arise because of lack of circulating vasopressin or insensitivity of the concentrating mechanism within the kidney to its action. Polyuria occurs in the following clinical circumstances:

(*a*) Diabetes mellitus in which an osmotic diuresis occurs because of glycosuria due to hyperglycaemia.

(*b*) Renal disease with uraemia in which the elevated concentration of urea in the blood acts as the osmotic diuretic.

(*c*) Conditions in which there is decreased responsiveness of the collecting ducts to vasopressin, e.g. in some cases of chronic renal disease, during the recovery phase of acute renal failure, in hypercalcaemia such as may arise in hyperparathyroidism, and in familial nephrogenic diabetes insipidus.

(*d*) The elimination of oedema, e.g. in recovery from heart failure or the nephrotic syndrome.

(*e*) Diabetes insipidus of neurohypophyseal origin in which there is diminished secretion of vasopressin.

(*f*) Inhibition of vasopressin secretion due to excessive drinking of fluid either from choice or from psychiatric causes, i.e. compulsive polydipsia.

Specific Gravity of Urine

The specific gravity of urine is defined as the ratio between the weight of a given volume of urine and the weight of an equal volume of distilled water. It is therefore a measure of the quantity of solids in solution and is an approximate measure of osmolality. For clinical purposes measurement of the specific gravity is made by a hydrometer (urinometer). In health, urea and sodium chloride are the main solutes contributing to the specific gravity of urine. In diabetes mellitus, on the other hand, the quantity of glucose in the urine may far outweigh the total of all the other solutes present: water containing 1 per cent glucose has a specific gravity of 1·004. Protein has almost the same effect in increasing the specific gravity as a similar quantity of urea. Urea, however, is present in a concentration of 2 g/100 ml in normal urine, while protein, even in the most severe cases of the nephrotic syndrome, is seldom present in such large quantities. Thus 4 g protein per litre, which gives a strong reaction with Albustix, raises the specific gravity by only 0·001. The specific gravity of urine varies with the nature and quantity of food eaten as well as with the amount of water or other fluid taken.

The maximal capacity of the kidneys to concentrate urine may be determined after either depriving the patient of fluid or by the injection of vasopressin, but if a random or pre-breakfast sample of urine is found to have a specific gravity of 1·020 or more there is clearly no need to carry out these tests. In health, fluid deprivation results in a rise in plasma osmolality which acts as a stimulus for production of antidiuretic hormone. The urine becomes progressively more concentrated as fluid deprivation is continued, and in experimental subjects increasing values for urine osmolality are found up to three days. This is far too long a period of time for clinical application but deprivation of fluid for at least 20 hours is necessary for consistently accurate results to be obtained in temperate climates. With this procedure urinary concentrations of above 800 mOsm, corresponding to specific gravity of from 1·022 to 1·040, are obtained in healthy individuals.

Reaction of the Urine and Acid Excretion

In health and on a normal diet, 40-80 mEq of acid are excreted daily in the urine. The greater part of this acid is excreted in buffered form, partly as dihydrogen phosphate, which constitutes the bulk of the titratable acidity of the urine, and partly as ammonium ions. A very small amount of free hydrogen ion is also excreted and it is this which is measured when the pH of the urine is determined. Little information is gained from the routine determination of urinary pH in random samples of urine. In certain circumstances the ability of the renal tubules to excrete hydrogen ions is depressed and the demonstration of this is of clinical significance. It is important to examine fresh specimens of urine since urea may decompose to form ammonia and give a false result if urine is left to stand. Infections of the urinary tract with organisms other than *Esch. coli* or tubercle bacilli also cause the urine to be alkaline owing to the breakdown of urea.

Estimation of the Tubular Capacity to Secrete Acid. The administration of ammonium chloride by mouth to the normal subject rapidly leads to a fall in the urinary pH and to a progressive rise in titratable acidity and in the amount of ammonium ions in the urine. Normally the pH of the urine is found to have fallen to less than 5·0 and this value is also reached in most patients with chronic renal disease. Failure to acidify the urine following the administration of ammonium chloride is characteristic of distal renal tubular acidosis occurring either as an inherited or acquired defect, and may also occur in potassium deficiency and in some patients with hypercalciuria and nephrocalcinosis. Additional information can be obtained by determining the titratable acidity and the rate of excretion of ammonium. These measurements give a value of the power of the renal tubules to secrete hydrogen ions in buffer form as monosodium dihydrogen phosphate and the ammonium ion. Titratable acidity and ammonia excretion are reduced in chronic renal insufficiency and in some patients with nephrocalcinosis. While titratable acidity is also reduced in potassium depletion and renal tubular acidosis, the power to excrete ammonia appears to be normal.

Measurement of Renal Clearance

The ability of the glomeruli to perform their function in health and disease may be estimated by the measurement of 'clearance'.

The term 'clearance' does not imply the complete removal of a substance from the plasma. It is an arbitrary, but quantitatively valid measurement which relates the amount of a substance present in the urine, produced over a unit of time, to its concentration in the plasma. It is measured from the following equation:

$C = \frac{UV}{P}$ in which C is the clearance, U is the concentration of the substance in the urine, P is the concentration of the substance in the plasma, V is the volume of urine in ml secreted per minute.

If a substance in the plasma passes freely through the glomerular filter, and is neither absorbed nor excreted by the tubules, the quantity excreted in the urine, UV, is identical with the quantity filtered by the glomeruli. The clearance of such a substance is therefore equal to the rate of glomerular filtration. Endogenous creatinine and the polysaccharide, inulin, appear to be excreted in this way and their clearances are used to estimate the rate of glomerular filtration, which for the average adult is about 120 ml per minute. Since urea is partly reabsorbed by the tubules its clearance is less than that of creatinine or inulin. The clearance of creatinine is determined by collecting urine over a 24-hour period and withdrawing one sample of blood during the day. It is advisable to check the accuracy of an abnormal result by repeating the test on several occasions.

Abnormal Constituents of Urine

1. **Protein.** The presence of protein in the urine, detectable by the use of Albustix or salicylsulphonic acid, is always of clinical significance. Proteinuria of this degree does not usually occur in disease of the lower urinary tract, though a small amount can be detected in severe urinary infection or obvious haematuria. Proteinuria almost invariably indicates the presence of parenchymal disease of the kidneys but its magnitude bears little relation to the degree of renal failure. In the absence of inflammation in the urinary tract, the protein is derived from plasma proteins which have penetrated the glomerular membrane in abnormally large amounts. Because of its smaller molecular size, albumin predominates over the globulins.

Small amounts of protein are usually found in the urine in severe chronic renal disease, in the course of febrile illness and in heart failure. Larger amounts of protein (e.g. 3 g/day or more) are found in the nephrotic syndrome (p. 595). Bence Jones proteins (p. 755) may be found in myelomatosis and rarely in other diseases of the reticulo-endothelial system.

POSTURAL (ORTHOSTATIC) PROTEINURIA. In a number of apparently healthy children and adolescents, and less commonly in adults, protein is excreted in the urine in variable but usually small amounts without associated disease of the kidneys. The urine formed while these individuals are recumbent is free from protein so that examination of the first specimen voided immediately on rising in the morning is normal. On the other hand urine formed while the individual is in the erect position or following exercise is found to contain protein. Tests of renal function show no abnormality.

There is evidence that the proteinuria in some cases is due to a rise in pressure in the renal veins produced by a kinking of the inferior vena cava as it passes through the diaphragm. It has been suggested that this kinking depends upon the forward rotation of the liver and the degree of fixation of the inferior vena cava to the posterior surface of the liver. Extreme lordosis produces proteinuria in the majority of young subjects. In others a reduction in blood flow known to occur on assuming the erect position may be an important factor. Hyaline casts, red cells, epithelial cells and leucocytes increase in proportion to the degree of proteinuria. Proteinuria of the orthostatic type is sometimes seen in the presence of renal disease. It should be regarded as a benign condition only if careful investigations fail to reveal any other abnormality.

2. **Blood.** Blood is found in the urine in a wide variety of clinical conditions; haematuria usually indicates serious disease of the urinary tract and the cause must always be sought. If an episode of haematuria is neglected and time is allowed for the symptom to recur in order to confirm the patient's observation, many potentially curable diseases will advance to an incurable stage. The appearance of the urine varies with the amount of blood and is normal to the naked eye when traces only are present. When larger amounts of blood are present the urine may be smoky in appearance, bright red or reddish-brown. The brown discolouration is due to the formation of acid haematin from haemoglobin.

Red blood cells are found in varying numbers in the urine in acute glomerulonephritis, infective endocarditis, malignant hypertension, polyarteritis, systemic lupus erythematosus affecting the kidney, renal tuberculosis, congenital polycystic disease, haemorrhagic diseases, renal infarction and trauma to the kidneys. Red cells occur in the urine also in inflammation and tumour of the kidney and of the urinary tract, in senile hyperplasia and carcinoma of the prostate, and in the presence of urinary calculi. They are absent or very scanty in nephrosclerosis, in chronic, minimal lesion and membranous glomerulonephritis and most cases of the nephrotic syndrome due to other causes.

Many of these conditions can be diagnosed by the presence of characteristic symptoms and signs in addition to haematuria. On the other hand when haematuria is the sole or presenting symptom the cause is likely to be one of the following conditions:

Renal	*Bladder*	*Prostate*
tumour	papilloma	benign enlargement
tuberculosis	carcinoma	carcinoma
	schistosomiasis	

When blood appears only at the beginning of micturition, the rest of the urine voided being clear, the source of bleeding is distal to the bladder. When blood is uniformly mixed with the urine, it may have come from any part of the urinary tract other than the urethra. Renal colic accompanying haematuria indicates that the bleeding is renal or ureteric in origin.

To establish the presence of small quantities of blood in the urine it is essential to examine microscopically the centrifuged deposit of a fresh specimen. If the specimen is not fresh, the hypotonicity of a dilute urine or the hypertonicity of a concentrated urine may destroy or deform the red cells. Even if the urine is obviously red it is necessary to demonstrate the presence of red cells microscopically, in order to distinguish haematuria from other rarer causes of discolouration of the urine with which there may be confusion. These are:

(*a*) *Haemoglobinuria*, which accompanies various rare intravascular haemolytic crises. The urine gives the chemical and spectroscopic tests for haemoglobin, but no red cells are present.

(*b*) *Phenolphthalein* in an alkaline urine. Phenolphthalein is an ingredient of many proprietary purgatives, and self-medication with alkalis and purgatives is common. As urine tends to become alkaline on standing it may turn pink if phenolphthalein is present. The addition of acid dispels the colour.

(*c*) *Beetroot*, *senna*, *dyes* used to colour sweets and a few other substances taken by mouth may redden the urine.

(*d*) *Acute intermittent porphyria* in which large amounts of porphobilinogen are excreted in the urine. Fresh urine from such cases may appear normal, but on standing for some hours a dark red colour may develop. The presence of porphobilinogen may be suspected from the red colour produced by the addition of Ehrlich's aldehyde reagent. In contrast to that produced by urobilinogen, this colour is not extracted by chloroform. The diagnosis should be suspected in the presence of one or more of the following clinical features: unexplained abdominal colic, polyneuritis and mental disturbance often precipitated by a drug such as phenobarbitone.

3. **Pus Cells and Bacteria.** Pus cells may be found in the urine in inflammation of any part of the urinary tract. The urine should always be examined under the microscope and cultured when urinary tract infection is suspected. In obtaining the specimen for culture it is best to avoid catheterisation. A midstream specimen should be obtained from both male and female patients, and a culture should be made of this within two hours. When this is not possible, the specimen should be refrigerated and sent to the laboratory within 24 hours.

4. **Urinary Casts.** Casts are cylindrical structures of microscopic size which are found in the urinary deposit. They are formed in the renal tubules by the coagulation of protein. Red blood corpuscles or epithelial cells may be impressed upon this matrix, producing blood and epithelial casts respectively; such casts are found in the early stages of acute glomerulonephritis and other diseases in which there is glomerular inflammation. Granular casts are formed by degeneration of the impressed cells. Epithelial and granular casts are indicative of inflammation and degeneration of the renal tubules. Hyaline casts are formed by coagulated protein without the addition of cellular elements and are found in chronic glomerulonephritis and occasionally in small numbers in normal urine, especially after vigorous exercise.

Although the number of cells and hyaline casts passed in the urine in the course of the day by the healthy adult is considerable, in practice microscopic examination of the centrifuged deposit reveals only an occasional cell or hyaline cast in each low power field.

5. **Bile and Urobilinogen.** These may also occur in the urine in abnormal amounts (p. 532).

Chemical Analysis of the Blood

With progressive impairment of renal function the composition of the body fluids becomes abnormal. These abnormalities may be detected by blood analyses. The products of metabolism which in health are excreted in the urine are retained in the blood, and the concentration of urea, creatinine and the anions such as phosphate and sulphate increases. Determination of the concentration of blood urea gives a useful indication of the degree of renal failure, but it should be remembered that this does not rise above the accepted normal maximum until renal function is reduced by at least 50 per cent. The diminishing capacity of the kidneys to secrete hydrogen ions results in their accumulation in the blood, and the severity of the consequent metabolic acidosis may be estimated by measurement of the concentration of bicarbonate. Estimation of plasma sodium, potassium, calcium and protein concentrations is of value in certain circumstances. A table of reference values for these and other biochemical factors, together with their SI equivalents, is given on page 1009.

Glomerulonephritis

The term ‘glomerulonephritis’ is used to describe a bilateral disease of the kidneys which usually affects all the glomeruli. In practice, cases can usually be placed in one of three clearly defined categories which are described below under the headings of proliferative, minimal lesion and membranous glomerulonephritis. In the past there has been difficulty in correlating the morbid histology with the clinical findings. The development of the technique of renal biopsy now permits a degree of clinicopathological correlation hitherto unattainable. In the early stages of all three disorders the histological pictures are distinct. In cases of proliferative glomerulonephritis which fail to recover completely, and in the later stages of membranous glomerulonephritis which is a chronic disease, the histological features become less clearly distinguishable. The fact that hypertension may accompany some stage of these two diseases complicates the pathology still further by the changes due to arteriolosclerosis. Although all are believed to be of immunological origin there is no evidence that the three types of glomerulonephritis are related aetiologically.

Proliferative Glomerulonephritis

This condition is characterised by a diffuse inflammation of the glomeruli of both kidneys. When the disease appears suddenly, the terms *acute glomerulonephritis* or *acute nephritis* are often applied; when the onset is more insidious it is usual to refer to the disorder as *proliferative glomerulonephritis.*

Aetiology. The majority of cases follow infection with haemolytic streptococci of Types 12, 49 or 57. This may occur as acute tonsillitis, scarlet fever or upper respiratory infection. However, it appears likely that some viruses and other micro-organisms may also be responsible. A latent period is usual, the features of glomerulonephritis developing one to three weeks after the infection has subsided. A previous history of an acute infection is more commonly obtained in children than in adults. The infection may be slight and even pass unnoticed, and there is no relationship between its severity and the probability of the development of the disease.

The condition occurs most commonly in childhood and adolescence but may occur at any age. As in the case of rheumatic fever and scarlet fever, the condition has become less common in recent years in affluent countries.

Pathology. The earliest lesion is a diffuse inflammation of the glomerular capillaries with variable swelling of the endothelial cells, proliferation of the mesangial cells and accumulation of polymorphonuclear leucocytes in the tuft and the glomerular space. There may be proliferation of the outer layer of Bowman's capsule to form epithelial crescents. In the majority of cases these changes disappear with clinical recovery and the kidney returns to normal.

In progressive cases the epithelial crescents, which arise as a result of the presence of red blood cells, fibrin and inflammatory exudate in Bowman's space, increase in size. Progressive fibrosis of crescents and glomeruli occurs and the glomerular capillaries gradually become obstructed, resulting in secondary degeneration in the tubules. Ultimately many nephrons may be replaced by fibrous tissue, leading to small contracted kidneys. It is possible that the degree of intravascular glomerular thrombosis plays a part in determining whether the condition resolves. This may be assessed by estimation of the breakdown products of fibrinogen and fibrin in the urine. Another factor influencing the outcome is excessive overgrowth of the mesangial cells and a failure on their part to fulfil their phagocytic role. The glomeruli become progressively compressed so that their function is impaired or extinguished.

Pathogenesis. The time interval between infection and the onset of acute nephritis is reminiscent of that between the injection of therapeutic serum and the onset of serum sickness. This interval, and the absence of bacteria in the renal lesions and the urine, suggest that the disease has an immunological basis. This view is supported by recent developments in immunological techniques which have shown a diminution in the concentration of serum complement and have demonstrated that circulating antibody complexes are deposited on the glomerular basement membrane (p. 34).

The appearance of generalised oedema, which is seen especially in the face, has given rise to a popular theory that there is generalised capillary damage throughout the body. The evidence suggesting this explanation has never been satisfactory, and it is now believed that the oedema is caused by fluid retention consequent on reduced filtration due to glomerular damage and to increased reabsorption of water and salt by the tubules. Heart failure may sometimes be a contributory factor.

Clinical Features. In children the onset is usually abrupt, the most constant features being puffiness of the face, low urinary output and blood-stained urine.

In addition there may be the general symptoms and signs of an acute infection, malaise, fever, anorexia, vomiting and headache. Breathlessness due to pulmonary oedema may be present and epistaxis may occur. Discomfort in the renal angles occasionally occurs. The pale puffy face gives an appearance which is almost pathognomonic. Oedema around the ankles may be detected if the patient is ambulant and in severe cases effusions occur into the serous sacs.

In adults the onset is usually more insidious with progressive tiredness and slowly developing oedema of the lower limbs. Virtually asymptomatic cases may be discovered after routine examination of the urine.

The cardiovascular system may be affected as indicated by hypertension, a rise in the jugular venous pressure, a slight outward displacement of the apex beat, a soft apical systolic murmur, reversed splitting of the second sound and bilateral basal crepitations.

In a few cases hypertensive encephalopathy occurs due to cerebral arteriospasm and oedema. These attacks are characterised by headache, restlessness, transient blindness or paresis, vomiting and generalised convulsions. There is no correlation between the occurrence of the seizures and the concentration of blood urea. Retinal examination may reveal papilloedema, haemorrhages and exudates.

URINE. The daily output is usually between 300 and 700 ml, due to reduction in the rate of glomerular filtration and increased tubular reabsorption. Anuria may occur in very severe cases. The urine may appear red or smoky owing to the presence of blood and is usually concentrated. Proteinuria is of moderate degree, seldom exceeding 4 g per day, but the amount present is out of proportion to the haematuria. Microscopic examination of the urinary deposit reveals erythrocytes, some leucocytes, and red blood cell, epithelial and granular casts.

Course and Prognosis. Complete recovery occurs in over 90 per cent of children who suffer from the disease. The prognosis is worse in adults and after middle age when recovery occurs in only about 50 per cent of cases. In most instances the acute manifestations lessen in the course of three to four days, the temperature, pulse rate and blood pressure falling to normal. Diuresis occurs, and the oedema, haematuria and number of casts in the urine diminish. Small amounts of blood may be present in the urine for 10 to 14 days, while proteinuria may persist for several weeks or months.

In a small number of cases the symptoms and signs persist for months or years. In some the proteinuria becomes massive and gross generalised oedema develops. Some authors call this stage subacute glomerulonephritis. Uraemia and acidosis slowly increase and the patient may die of renal failure while oedema persists.

In about 10 per cent of cases hypertension and haematuria subside and the patient apparently regains normal health. Proteinuria however persists, and after many years chronic glomerulonephritis hypertension and renal failure develop.

Rarely, marked hypertension, extreme oliguria, recurrent convulsions and death may occur within a few days from acute cardiac failure and pulmonary oedema or in two or three weeks from uraemia. Treatment by dialysis has improved the mortality in this group but it still remains high.

Renal Function Tests. In the early stages renal concentrating power is usually unimpaired, and the specific gravity of the urine is high. The rate of glomerular filtration is reduced and the concentration of urea in the blood is raised. A moderate degree of acidosis is usual. When recovery occurs the filtration rate rises and the blood urea concentration falls to normal.

Diagnosis. Acute glomerulonephritis should be distinguished from:

1. Angio-oedema, in which sudden swelling of the eyelids is a frequent feature. This condition is usually associated with swelling of the lips or tongue; urinary abnormalities are absent. In addition, the patient may be known to be an allergic subject, similar attacks may have occurred previously, and eosinophilia is often present.
2. Henoch-Schönlein purpura (p. 760) in which the hypersensitivity often involves the glomeruli with resulting haematuria; it is suggested by the presence of purpura and swollen joints.
3. Polyarteritis and systemic lupus erythematosus are both conditions in which the glomeruli may be affected with consequent haematuria and proteinuria. Red blood cell casts may also be found in the urine. Other organs of the body are usually involved in the pathological process, and the diagnosis of these two diseases is suspected on this basis. Polyarteritis and systemic lupus erythematosus are occasionally confined to the kidney, when renal biopsy is necessary to establish the diagnosis.
4. Goodpasture's syndrome is a rare condition in which acute proliferative glomerulonephritis is associated with pulmonary capillary haemorrhage and haemoptysis. The cause is unknown but an abnormal immunological mechanism is involved (p. 32).
5. Acute pyelonephritis, in which oedema is absent while pain and tenderness in the region and frequency of micturition may be prominent. The urine contains micro-organisms, more pus cells than red blood cells and red blood cell casts are absent.
6. Haematuria due to tuberculosis or tumours of the kidney or urinary tract. In these conditions oedema does not occur and there are no cellular casts in the urine.
7. Infective endocarditis, in which microscopic haematuria is a valuable diagnostic sign, and uraemia may develop.
8. Acute recurrent focal nephritis. This is a condition of unknown, but probably multiple aetiology in which recurrent episodes of haematuria occur over a period of months or years. There are no other symptoms or signs of acute proliferative glomerulonephritis or Henoch-Schönlein purpura. The diagnosis is made by renal biopsy in which mesangial cell proliferation is found affecting only a proportion of glomeruli. Repeated episodes may lead to progressive glomerular destruction with renal failure and hypertension.

Treatment. There are three principal needs in the treatment of acute proliferative glomerulonephritis, namely (1) rest and warmth, (2) dietary regulation, and (3) the elimination of infection.

REST AND WARMTH. The patient should be kept warm in bed and protected from cold and draughts; rest in bed should be maintained until haematuria, hypertension, oedema and proteinuria have disappeared, and this may occur in from two to four weeks. Opinions vary as to how long rest in bed should be enforced in those cases which show persistent abnormalities in the urine beyond this time. When the patient feels well, but protein and red cells in the urine fail to show any diminution over a period of several weeks, it is doubtful whether further rest in bed is of benefit and the patient should be allowed up and encouraged to resume activities gradually.

DIETARY REGULATIONS. There is no evidence that modifications of the diet make any significant difference to the healing process in nephritis, but protein restriction controls the degree of uraemia. Complete restriction of protein with an adequate energy intake from carbohydrate and fat ensures minimum protein breakdown. For most cases, however, reduction of the protein intake to 20-40 g/day appears to be satisfactory.

In addition to protein restriction, treatment should be directed to maintaining fluid and electrolyte balance. In cases of *mild to moderate* severity:

1. *Fluid* should be restricted while oedema is present to $\frac{1}{2}$ litre per day plus the volume of the previous day's output. If there is evidence of pulmonary oedema, fluid should be withheld entirely.
2. *Food* should be given in such quantities as the patient desires, but consisting mainly of carbohydrate and fat, e.g. bread, biscuits, cereals, jam, syrup, sugar and vegetables. Not more than half a pint of milk per day may also be taken. Sufficient protein is present in such foods to reduce the breakdown of body protein for essential needs to a low level (Diet 13, p. 1003).
3. *Salt* should not be used in cooking nor added to food. If the oedema is severe a low salt diet should be given (Diet 8, p. 998).

In the occasional rare case of *severe* nephritis with anuria or extreme oliguria which shows no improvement on the measures mentioned above within three or four days, the regime described on page 610 should be adopted.

When hypertension and haematuria have subsided and diuresis has occurred, a light diet with a moderate restriction of protein (an egg at one meal and a small helping of fish, or meat at another meal (Diet, 14, p. 1004)) is given for a few days before the resumption of a normal diet.

ELIMINATION OF INFECTION. Streptococcal infection should be treated by giving an antibiotic such as benzylpenicillin in a dose of 300 mg (500,000 units) twice daily by intramuscular injection for five days.

Removal of infected tonsils or other septic foci should be delayed until convalescence is advanced, as operation may be followed by an exacerbation, especially if carried out during the acute stage. However, in a few cases of nephritis with persistence or repeated recurrence of symptoms and signs, these features may disappear only after the removal of a focus of chronic infection, e.g. apical teeth abscesses. In the event of operative treatment being needed, benzylpenicillin should be given on the day of operation and for three days after it.

OTHER MEASURES. Hypertension does not require treatment in the majority of cases; the treatment of hypertensive encephalopathy is described on page 281. Attempts to influence the course of the disease by the use of immunosuppressive drugs have not been successful and the use of anticoagulants in the progressively severe case remains under trial.

Minimal Lesion Glomerulonephritis and Membranous Glomerulonephritis

Minimal lesion and membranous glomerulonephritis are conditions associated with an increase in the permeability of the glomerular basement membrane. This leads to proteinuria which is often so severe that hypoproteinaemia and oedema develop. The two conditions are described together because clinically they are usually indistinguishable at the outset.

Aetiology. The aetiology of both types of glomerulonephritis is unknown. Unlike proliferative glomerulonephritis neither disease is preceded by any recognisable infection. There is little doubt that an abnormal immune process (p. 34) plays a part but there is no proof that such a mechanism is responsible for initiating the diseases.

Pathology. Renal tissue obtained by biopsy shows two easily distinguishable lesions. In membranous glomerulonephritis the histological appearances consist of a diffuse hyaline thickening of the glomerular capillary walls with little or no evidence of inflammation. As the disease progresses the thickening becomes more severe and the glomerular tufts are converted into structureless hyaline tissue. Immunofluorescent studies show that while immunoglobulins are deposited in the basement membrane, there is little or no mesangial cell proliferation characteristic of proliferative glomerulonephritis. In minimal lesion glomerulonephritis, the glomeruli show no lesion when examined by light microscopy. However, abnormalities of glomerular structure involving especially the epithelial cells are revealed by the electron microscope. The evidence suggests that this condition does not progress to glomerular destruction as is usually the case with membranous glomerulonephritis.

Clinical Features. The diseases are insidious in onset. If the proteinuria is slight they may persist without symptoms and remain undetected for months or years. When proteinuria increases in severity oedema occurs and it is in this way that attention may be drawn to their existence. The oedema is generalised, involving first the subcutaneous tissue and later the serous sacs and lungs. The face presents a pale and puffy appearance. The general health may remain good for some considerable time but eventually becomes progressively impaired, with increased liability to infection of the oedematous tissues or the serous cavities.

The urine contains protein in moderate amounts though as much as 30 g may be excreted per day in occasional patients. Granular and hyaline casts are seen on microscopic examination, red cells being scanty or absent.

At first chemical examination of the blood shows little or no increase in urea.

Plasma cholesterol is raised commonly to 300-500 mg per 100 ml and the plasma and ascitic fluid may look milky due to an increase in fat and β-lipoproteins. Total plasma proteins are greatly reduced, e.g. to 3-4 g per 100 ml. There are quantitative changes in the various globulin fractions, but the chief reduction affects albumin. Proteins of larger molecular weight, especially α_2-globulin, are retained in the blood and hence are increased relative to the other plasma proteins. The resulting fall in colloid osmotic pressure of the plasma is mainly responsible for the massive oedema which is the prominent clinical feature. The ensuing oligaemia stimulates the secretion of aldosterone which promotes further electrolyte and water retention and sometimes potassium loss.

In the early stage of the diseases renal function tests reveal no impairment of glomerular filtration rate or of the ability to concentrate urine.

Course and Prognosis. In the majority of cases the oedema persists for months or years, with occasional spontaneous but temporary remissions. Prior to the use of effective diuretics, antibiotics and corticosteroids, recovery rarely occurred. The majority of patients died either from intercurrent infection in the oedematous phase or from renal failure. There is now ample evidence that in patients with minimal lesion glomerulonephritis, immunosuppressive treatment causes the proteinuria to subside and the condition to resolve. In membranous glomerulonephritis, however, the prognosis is less favourable. Arterial hypertension and hypertensive retinopathy develop and progressive renal destruction ultimately reduces the rate of glomerular filtration in the majority of cases. Proteinuria diminishes, and consequently the plasma proteins rise and oedema becomes less. There is gradual impairment of renal function as the disease progresses to chronic glomerulonephritis with uraemia (p. 597).

Differential Diagnosis of the Nephrotic Syndrome. The term 'nephrotic syndrome' is used to describe the clinical state of hypoproteinaemic oedema associated with marked proteinuria irrespective of its aetiology. Minimal lesion glomerulonephritis is the most common cause of the nephrotic syndrome in children and is responsible for about 20 per cent of cases in the adult. Membranous glomerulonephritis is more common in adults and both must therefore be distinguished from other renal disorders which give rise to a similar clinical picture. Sometimes the aetiology of the nephrotic syndrome is obvious from the presence of other clinical features of the causative disease. In many patients it is necessary to carry out a renal biopsy in order to make the diagnosis. Causes of the nephrotic syndrome apart from these two types of glomerulonephritis are as follows:

(*a*) *Proliferative glomerulonephritis* is occasionally associated with marked proteinuria and massive oedema. In many patients the clinical history and the course of the disease are sufficient to make this diagnosis clear, but in others the true nature of the syndrome is detected only after renal biopsy.

(*b*) The nephrotic syndrome associated with *diabetic nephropathy* is discussed on page 704.

(*c*) *Amyloid disease* is usually secondary to rheumatoid arthritis, multiple myeloma, tuberculosis or chronic suppuration. It gives rise to proteinuria as a result of the deposition of amyloid material in the glomerular capillaries. Renal biopsy is usually necessary to provide histological evidence of amyloid infiltration.

(*d*) *Poisoning* due to *drugs*, e.g. mercury, gold and troxidone.

(*e*) *Renal vein thrombosis* is a rare cause of the nephrotic syndrome. It should be suspected when proteinuria occurs in a patient with evidence of deep venous thrombosis in the lower limbs or if an illness is complicated by pain in the loins and the subsequent development of the nephrotic syndrome.

(*f*) Occasionally the syndrome develops as the presenting feature in the course of *systemic lupus erythematosus*. It also may occur in *polyarteritis*.

(*g*) *Quartan malaria* is an important cause of the syndrome in children in parts of Africa (p. 967).

(*h*) Occasionally it arises in association with *tumours* when it may be due to circulating autoantibodies being deposited in the glomerulus.

The nephrotic syndrome must also be distinguished from:

(*a*) *Cardiac failure* with severe oedema, in which dyspnoea is present, the venous pressure is increased, signs of underlying cardiac disease are present, oedema is usually absent from the face, and proteinuria is less severe.

(*b*) *Chronic glomerulonephritis and nephrosclerosis*, in which oedema is due to cardiac failure, resulting from hypertension, and there is impairment of renal concentrating power.

(*c*) *Hypoproteinaemic oedema*, due to causes other than loss of protein in the urine, namely impairment of intake, digestion, absorption or synthesis of protein and in protein losing enteropathy.

Treatment. This is directed toward the relief of oedema and the control of proteinuria.

RELIEF OF OEDEMA. 1. Protein intake. So long as the blood urea is not elevated, a liberal intake of protein is desirable in an attempt to make good the urinary loss of protein. At least 90-100 g protein per day should be given. This may be supplemented with Casilan or Lonolac which are salt-free protein concentrates (Diet 12, p. 1002).

2. Salt intake should be restricted by prohibiting extra table salt, avoiding salty foods and reducing the amount used in cooking. Although drastic salt restriction occasionally produces dramatic results, 'salt-free' diets are so unappetising that patients will not tolerate them for more than a few weeks.

3. Diuretics are of great value in controlling the oedema. One of the thiadiazine diuretics, or frusemide or ethacrynic acid may be equally effective (p. 195).

4. If oedema is resistant to these measures relief may be obtained by giving plasma, salt-free albumin or dextran intravenously.

5. Spironolactone is indicated in patients who show marked features of secondary aldosteronism, e.g. hypokalaemic alkalosis.

CONTROL OF PROTEINURIA. *Corticosteroids* (p. 669) provide the main chance of cure in the treatment of minimal lesion glomerulonephritis. In the majority of cases this treatment abolishes proteinuria. Prednisolone should be given in doses of 1 mg/kg day for about three weeks and then reduced to about one-third of this dose and continued for at least six months.

In a minority of patients with minimal lesion glomerulonephritis the condition relapses after treatment when prednisolone is stopped. Such individuals are then best treated with *cyclophosphamide* given in doses of 3 mg/kg body weight for three to four months.

Corticosteroids, cyclophosphamide and other immunosuppressive drugs are ineffective in membranous glomerulonephritis.

Chronic Glomerulonephritis

Aetiology. Chronic glomerulonephritis develops when acute proliferative glomerulonephritis becomes progressive and in many cases of membranous glomerulonephritis. Frequently, however, no history of either disease is obtained and in these, post-mortem studies of the kidney suggest that the pathological change has been developing insidiously over many years. Both conditions lead to chronic renal failure (p. 607).

Pathology. The kidneys are small; the capsules strip with difficulty, leaving a granular surface; the peripelvic fat is increased and there is great reduction of parenchyma. The normal distinction between cortex and medulla is obscured.

On microscopical examination there is fibrosis or hyalinisation of most of the glomeruli with fibrous replacement of many tubules. Remaining nephrons may show hypertrophy and arteriolosclerosis is usually present.

Pathogenesis. The clinical features of chronic glomerulonephritis are attributable to the effects of chronic renal failure combined usually with arterial hypertension. As renal failure develops, the composition of the body fluid becomes abnormal, particularly with regard to its water and salt content, its acid-base equilibrium, and the concentration of nitrogenous compounds which are normally excreted by the kidney. These alterations ultimately combine to produce the clinical picture of severe uraemia which is the terminal stage of renal failure.

Clinical Features. A history of acute glomerulonephritis or of the nephrotic syndrome is obtained in some cases. The earlier stages of the disease may be unattended by symptoms but may come to light only by discovery of proteinuria or hypertension during the course of a routine examination. Later, because of the widespread consequences of renal failure, the symptoms and signs are referable to almost every system and patients suffering from the disease present with complaints which at first sight may not suggest their renal origin. The patients may seek medical advice because of polyuria, thirst, loss of energy, weakness, nausea, vomiting, or diarrhoea. Polyuria develops both because of diminished power for tubular reabsorption of water and because the elevated blood urea produces an osmotic diuresis. Anaemia is the main cause of the loss of energy and it is usually normocytic. The high blood pressure may have been detected in the course of a general examination or the patient may have sought advice for headache, loss of vision or breathlessness or because of the occurrence of cerebrovascular insufficiency.

As the disease progresses, renal function deteriorates and uraemia increases.

The blood concentration of urea and other nitrogenous compounds steadily rises. The patient looks more ill and the complexion is sallow, often accompanied by a yellow-brown discolouration attributed to the retention of urinary pigment. With the exception of those who develop cardiac failure from hypertension and those in whom the chronic stage of membranous glomerulonephritis has followed rapidly upon the initial oedematous stage, the patients are not only free from oedema but usually exhibit signs of water and salt depletion. The skin and tongue are dry and the blood pressure may fall from its previous high level. Acidosis contributes to the dyspnoea and the respirations are deep (Kussmaul's respiration). Hiccough, muscular twitchings, fits, drowsiness and coma may occur. A tendency to bleed may develop in the terminal phase, as evidenced by epistaxis, bleeding gums, bruises, purpura, haematemesis and melaena. Hypertensive retinopathy of any degree may be present and visual impairment may result from numerous hard exudates arranged in star shape around the macula. Some patients complain of vague muscle or bone pain and in a few cases this becomes severe. Peripheral neuropathy due to uraemia also occurs.

Radiological examination occasionally reveals the appearances of osteomalacia, osteitis fibrosa (p. 649) and areas of osteosclerosis. Osteomalacia is due to the development of resistance to the action of vitamin D which probably owes its origin to failure by the kidney to convert vitamin D taken in the diet to the active metabolite (p. 136). In young individuals this interferes with normal growth and the condition has been called renal rickets. Osteitis fibrosa arises as a result of secondary hyperparathyroidism, the parathyroid glands being stimulated by the low concentration of plasma calcium. The cause of osteosclerosis is unknown.

Laboratory Data. During the early stages of the disease, and before nitrogen retention in the blood is detectable, the urine is found to contain protein, usually in small amounts; red blood cells and granular and hyaline casts are present in small numbers. Glomerular filtration may be reduced to less than 10 per cent of normal and there is a gradual rise in the concentration of plasma urea, creatinine and phosphates. The ability of the kidneys to form concentrated or dilute urine is impaired. Ultimately this power is lost completely and the urine is of a fixed specific gravity (1·010). The plasma concentration of bicarbonate diminishes as acidosis occurs. The plasma concentrations of sodium and calcium are frequently lowered. Potassium occasionally accumulates in the blood and is one of the factors causing death by its effect on the heart.

Course and Prognosis. The disease progresses steadily over months or years to a fatal termination. The course may be punctuated by exacerbations of acute glomerulonephritis which hasten the progress of the disease. When nitrogen retention and acidosis are severe, the outlook is grave and most patients die in a few months or a year. Papilloedema is a bad prognostic sign and unless treatment with hypotensive drugs is instituted before uraemia becomes severe, most patients who show it die within a few months. The cause of death is generally uraemia frequently complicated by infection to which such patients are susceptible; in other cases the patient dies from a cerebral haemorrhage, cardiac failure or myocardial infarction. A terminal non-bacterial pericarditis is common. Haemorrhage from any site or enterocolitis are also ominous features.

Diagnosis. The distinction between chronic glomerulonephritis and other causes of chronic renal failure with hypertension is difficult and may be impossible. A similar clinical picture may arise in the following diseases.

1. Other conditions which primarily affect the glomeruli with their eventual destruction include polyarteritis, systemic lupus erythematosus, amyloid disease and diabetes mellitus. Patients suffering from these conditions may die ultimately of renal failure and uraemia.
2. Essential hypertension may occasionally lead to nephrosclerosis and uraemia. This should be suspected if there is a clear family history of high blood pressure; also in the malignant phase of hypertension from any cause evidence of renal disease is invariably present and renal failure is rapidly progressive.
3. Congenital polycystic disease of the kidneys may be diagnosed by the family history, by palpation of the enlarged, firm and irregular kidneys and by pyelography.
4. Chronic pyelonephritis is more common in women, and hypertension may be absent. There may be a history of acute pyelonephritis and organisms can sometimes be cultured from the urine.
5. Bilateral hydronephrosis may be confirmed by retrograde pyelography.
6. Congenital renal hypoplasia with bilateral small kidneys is occasionally the cause of death from uraemia in children.

Treatment. Although the natural history of the disease cannot be altered and there is progressive deterioration in renal function, the patient's health and feeling of well-being may be considerably improved with suitable treatment.

Diet. When there is nitrogen retention the onset of severe uraemia may be delayed by restricting protein intake to 40 g per day and by ensuring an adequate intake of carbohydrate and fat (Diet 13, p. 1003). In the later stages when the blood urea concentration rises to 200 mg/100 ml further protein restriction to 20 g/day is indicated. It is best to provide this as first class protein in the form of meat, milk and eggs and to avoid protein of lesser biological value in vegetables and cereals.

Fluid. Fluid restriction is contraindicated since, in view of the impaired concentrating power, a large volume of urine is needed to excrete end-products of metabolism. Except in the presence of cardiac failure a fluid intake sufficient to produce at least 2½ litres of urine per day should be advised.

Salt. In the absence of oedema, cardiac failure or arterial hypertension, salt restriction is contraindicated. In a few cases of chronic nephritis there is an excessive loss of salt in the urine due to a failure of tubular reabsorption, and this may be aggravated by an enforced high fluid intake. Water and salt depletion occur and this aggravates the uraemia (p. 607). Clinical improvement results in such cases from the addition of 5-10 g salt per day. The limit to the additional salt is set by the occurrence of systemic or pulmonary oedema, or by an aggravation of the hypertension. Sodium bicarbonate should be substituted in part for sodium chloride when acidosis is severe and giving rise to symptoms.

When nausea, vomiting or coma make it impossible to control water and salt depletion and acidosis by oral administration, fluid and electrolytes should be given by intravenous infusion. The volume of fluid required depends upon the severity of the salt and water depletion and the degree of acidosis (p. 202). An average amount for a case of moderate severity is 5 litres given in 24 hours, one part of isotonic sodium bicarbonate, two parts of isotonic sodium chloride and two parts 5 per cent glucose. The infusion should be continued until the bicarbonate concentration of the blood has been increased, if possible to within the normal range and until the patient is adequately hydrated.

Infection. Obvious foci of infection, e.g. tonsils, infected sinuses or root abscesses should be removed in order to reduce the likelihood of an exacerbation of acute glomerulonephritis. Antibiotics, as with other medication, must be used with special care in the presence of chronic renal failure, notably benzylpenicillin (p. 98), tetracyclines (p. 101), the aminoglycosides, streptomycin and kanamycin (p. 102) and cephaloridine (p. 99).

Anaemia. This should be treated by slow blood transfusions though it is probably not desirable to increase the concentration of haemoglobin above 8·5 g, as a rapid rise in haematocrit causes a fall in renal plasma flow and a temporary aggravation of the uraemia; oral or parenteral iron therapy is ineffective unless there is evidence of a complicating iron deficiency.

Nausea, Hiccoughing or Vomiting. This may be relieved with chlorpromazine (25 mg intramuscularly).

Bone Pain. If bone pain is severe and if the dominant radiological picture is that of osteomalacia, vitamin D should be given orally in doses of up to 5 mg calciferol daily for some weeks. The treatment should be controlled by chemical estimations of plasma calcium and alkaline phosphatase, for there is a significant risk of producing hypercalcaemia and calcification of the tissues.

Cardiovascular Complications. The presence of uraemia is no contraindication to the treatment of co-existing hypertension provided that care is taken to see that antihypertensive treatment does not cause a rise in the concentration of blood urea. The choice and use of drugs should be made according to the recommendations given on pages 278-280. Digoxin is normally excreted in the urine, and hence in renal failure the maintenance dose should not usually exceed 0·25 mg three times per week.

HAEMODIALYSIS AND RENAL TRANSPLANTATION. Within the last few years it has been possible by repeated intermittent haemodialysis to preserve the life of some patients with chronic renal failure who are devoid of all renal function. Facilities are limited but are likely to increase in the future; such treatment is possible at home in selected cases, where survival of up to 10 years is not uncommon.

The practicability of transplantation of a normal kidney from a healthy donor or a cadaver to patients with chronic irreversible renal failure is also under active investigation. Discreet enquiries should be made concerning the existence of an identical twin. If the healthy twin is willing to act as a donor the prospects of renal transplantation being successful are good. Most kidney transplantations are carried out using either kidneys from living but less closely related donors or from cadavers. It is customary to try to select donor kidneys on the basis the pattern of HL-A compatibility (p. 16), but there is little evidence that this is of importance in cadaver transplants. After two years the average survival rate is about 50 per cent, but the post-operative course is complicated by the need to give immunosuppressive drugs such as prednisolone, azathioprine or antilymphocytic serum.

Urinary Tract Infection

Infection of the urinary tract is an extremely common clinical problem. The infection may involve the urethra, the bladder, the ureters and the kidneys themselves. In any individual case it is difficult on clinical grounds to be certain of the extent of the invasion of the various parts of the urinary tract. In recent years the tendency has been to assume that the kidneys and the upper urinary tract are involved in every case, even when the symptoms of the infection are those solely of cystitis or urethritis. However, many patients develop recurrent symptoms of lower urinary tract infection without apparently suffering deterioration of renal function in later life.

Acute Pyelonephritis

This is characterised by an acute inflammation of the parenchyma and pelvis of the kidney. The term 'pyelitis' is still used, but is inaccurate as the inflammation involves the renal tissue as well as the pelvis. The disease may be unilateral or bilateral.

Aetiology. Acute pyelonephritis is commonly associated with some obstruction in the urinary tract. In view of the importance of preventing chronic pyelonephritis, the existence of a predisposing lesion should be suspected in every case. In men this is commonly due to ① prostatic enlargement, in ② pregnant women to obstruction by the uterus and atonia of the ureters due to the action of ③ progesterone, and in ④ children to congenital malformation of the urinary tract. ⑤ Calculi, foreign bodies or tumours may also be responsible. Pyelonephritis may occur in infancy and in adult women, however, without evidence of an obstructive lesion. In most cases the infection ascends via the ureter but in some it is blood borne. About 75 per cent of the infections are due to *Esch. coli*, the remainder being mostly due to streptococci, staphylococci or the Proteus group of organisms.

The predominance of urinary infections in the female suggests that the anatomical relation of the short urethra to the rectum is a predisposing factor. Catheterisation of the bladder is particularly liable to introduce organisms into the urinary tract, and this procedure may be responsible for the later development of acute or chronic pyelonephritis in some patients. Catheterisation should be reduced to the minimum and when indicated should be carried out with strict aseptic precautions.

Pathology. The renal pelvis is acutely inflamed and there is often a coincident inflammation of the bladder. In those cases with macroscopic involvement of the renal parenchyma, groups of small abscesses may be seen on the surface of the kidney when the capsule has been stripped. On section, small cortical abscesses and linear streaks of pus in the medulla are often evident. On histological examination a focal infiltration of the renal parenchyma by polymorphonuclear cells is evident.

Clinical Features. In many cases there is a sudden onset of pain in one or both loins, radiating to the iliac fossae and suprapubic area. There may be dysuria (difficult or painful micturition) and strangury (a painful desire to pass urine though the bladder is empty), with the frequent passage of small amounts of scalding, usually cloudy urine, due to an associated cystitis. The temperature rises rapidly to 38-40° C., with the general manifestations of fever. A rigor may occur, and there may be vomiting. Tenderness and muscular guarding may be present in the renal angle and the lumbar region. There is a leucocytosis. The urine in *Esch. coli* infections is nearly always acid; in other infections it may be acid or alkaline. On microscopic examination there are numerous pus cells and organisms, some red cells and epithelial cells. When the organisms are motile Gram-negative bacilli and the urine is acid in reaction, the infection may be assumed to be due to *Esch. coli.*

Acute pyelonephritis may occur with few or no symptoms referable to the urinary tract. This is particularly the case during pregnancy. Routine culture of a midstream specimen of urine has revealed the presence of asymptomatic bacteriuria in about 7 per cent of all pregnancies during the early months. If no antibiotics are given progression to acute pyelonephritis occurs in about 40 per cent of such cases, and this is rare in those in whom the urine was sterile at the original examination. Investigation by intravenous pyelography after the termination of pregnancy shows a high incidence of abnormalities of the urinary tract in those women with bacteriuria. Suppressive chemotherapy at the asymptomatic stage has been found to prevent the development of acute symptoms and progressive renal damage.

Pyelonephritis in children, like infections of the throat and middle ear, often presents as a fever without any localising symptoms. The initial feature may be a convulsion. In the feverish child, particular attention should be paid to these sites and the urine should be examined for pus cells and organisms.

Diagnosis. Acute pyelonephritis should be distinguished from:

1. Acute appendicitis, salpingitis, cholecystitis and diverticular disease, especially by the absence of pus and organisms in the urine.

2. Diaphragmatic pleurisy, with or without pneumonia. Pain is usually made worse by coughing or a deep breath. Tenderness with guarding similar to that occurring in pyelonephritis may be present, but there are no abnormalities in the urine and abnormal physical signs may be detected in the chest.

3. Perinephric abscess due to infection by *Staph. aureus*. The illness is severe and the characteristic clinical features are pain and tenderness in the renal region, high remittent fever and polymorphonuclear leucocytosis. Urinary symptoms are absent and there are usually no pus cells or organisms in the urine. Oedema may obliterate the normal hollow in the loin, and an abscess may eventually point in the loin or groin, or it may rupture into the peritoneal or pleural cavity. Careful enquiry frequently elicits the history of a recent boil.

Course and Prognosis. With adequate treatment the disease subsides rapidly in the great majority of cases. Fever, pain, frequency and dysuria disappear in a day or two. The urine usually becomes sterile within a few days.

In some cases, although the acute symptoms subside, a low-grade infection may persist, and the disease may pass into the chronic stage. More rarely the disease may be severe and cause necrosis of the papillae (acute necrotising papillitis). Fragments of renal tissue are then excreted in the urine and can be identified histologically. This complication, which may lead to renal failure, is particularly liable to occur in diabetic patients and in those addicted to phenacetin (p. 620). In view of the frequency of acute pyelonephritis, the curable nature of the condition, and the fact that chronic pyelonephritis is a common cause of renal failure and hypertension, the importance of adequate treatment of the acute stage cannot be overstressed.

Treatment. The patient should be confined to bed and the general measures for the treatment of fever applied (p. 56). The precise treatment depends upon the infecting organism and its sensitivity, and a midstream specimen of urine should be sent to the laboratory before treatment is begun. This specimen should reach the laboratory within two hours of voiding or be refrigerated at 4° C. for a period not exceeding 24 hours. Since infection is usually due to *Esch. coli* it has been customary for many years to start treatment with sulphadimidine in doses of 1 g three times a day after a loading dose of 2 g before the results of urine culture are available. On the other hand the sulphonamides are bacteriostatic drugs to which an increasing number of strains of *Esch. coli* are becoming resistant and they may induce serious adverse effects. Co-trimoxazole has been shown to be very effective in the acute attack but should not be given to pregnant women. Some authorities believe that cycloserine is the drug of choice in doses of 250 mg twice daily for 14 days for initial treatment. Its advantages lie in the fact that resistance is rare and toxic effects are fewer than with sulphonamides. It should not be given in the presence of renal failure as it accumulates in the body and may cause epileptic fits. Whatever drug is employed a second midstream specimen of urine should be sent to the laboratory from four to six weeks after the completion of the initial course of treatment to make sure that the infection has been eradicated. If this has not been accomplished further treatment with the appropriate antibiotic must be given, depending on the bacteriological findings. In the very severe case, and if septicaemia occurs, kanamycin or gentamicin are the drugs of choice. Ampicillin is of value in proteus infections and carbenicillin, gentamicin or polymyxin E in infections with *Ps. aeruginosa.* Dosage of these antibiotics is given on pages 97 to 102.

In every case the possibility of calculus, an obstructive lesion of the urinary tract or renal tuberculosis must be considered and treated if found.

Chronic Pyelonephritis

Aetiology. The disease may follow an attack of acute pyelonephritis which has been treated inadequately. It may be caused also by infection above an obstruction to the urinary tract, e.g. calculus, stricture or prostatic disease.

Other cases may follow cystitis due to stasis as a result of a cystocele or interference with the innervation of the bladder, e.g. in paraplegia or disseminated sclerosis. *Esch. coli* is the organism responsible for most cases. Other infecting agents are proteus, *Ps. aeruginosa*, staphylococci, etc. In conditions in which the outflow tract of the bladder is deranged, reflux of urine into the ureters may occur during micturition. It is not known if vesico-ureteric reflux occurs in the absence of such a lesion nor to what extent it contributes to the development of pyelonephritis. Chronic pyelonephritis also occurs in conditions leading to nephrocalcinosis (p. 613).

Pathology. The changes may be unilateral or bilateral, and of any grade of severity. The fully developed case usually shows gross scarring of the kidneys, which may be much reduced in size with narrowing of the cortex and medulla. Microscopically there is patchy fibrosis with chronic inflammatory cell infiltration, tubular atrophy, periglomerular fibrosis and eventual disappearance of nephrons. The arteries and arterioles may show sclerosis and narrowing.

Clinical Features. In many cases no symptoms arise directly from the renal lesions, and the patient may consult the doctor because of lassitude, tiredness and vague ill-health or for symptoms of uraemia or arterial hypertension. The discovery of hypertension or proteinuria on routine examination may be the first indication of the presence of the disease. Symptoms arising from the urinary tract, however, may also be present and include frequency of micturition, dysuria and occasionally aching lumbar pain. The urine may contain pus cells, a small amount of protein and many epithelial cells, though in some cases it may be normal.

Diagnosis. In all cases of chronic pyuria, investigations such as rectal or vaginal examination, cystoscopy and pyelography must be carried out to discover the nature of any underlying mechanical factor causing obstruction to the flow of urine and to determine the extent of the infection. Chronic pyelonephritis should be distinguished from renal tuberculosis by cystoscopy, pyelography and bacteriological examination of the urine. In the later stages, when hypertension and uraemia have developed, the condition may be difficult to distinguish from chronic glomerulonephritis and nephrosclerosis. The presence of pus and organisms in the urine and a past history of frequency and dysuria support the diagnosis of chronic pyelonephritis.

Course and Prognosis. The course is usually a long one and may be punctuated by acute exacerbations. The infection is difficult to eradicate, even when underlying mechanical obstructions are found and relieved. Some cases progress to chronic uraemia, which may be alleviated for a year or two by treatment. In elderly people, in diabetic patients and in cases of tabes dorsalis or paraplegia, the infection may become fulminating and be the immediate cause of death.

Complications. Hypertension and uraemia have been discussed above. Pyonephrosis may occur, especially in the presence of renal calculi. It is characterised by persistent lumbar pain, intermittent pyrexia, often with rigors, emaciation, pyuria, and, if both kidneys are involved, uraemia. One or both kidneys may become palpable.

Treatment. Medical treatment of chronic pyelonephritis is similar to that described for the acute disease. The chronic infection is usually more difficult to eradicate. Attempts should be made to remove obstructive lesions or renal calculi by appropriate surgical procedures. An antibiotic to which the organism is sensitive should be given for 14 days (p. 603). If the infection is not eradicated suppressive antibiotic treatment may be required for many months, the antibiotic used being indicated by the changing pattern and sensitivity of the organisms in the urine (p. 108). Ampicillin and cycloserine are valuable for this purpose but cycloserine should be avoided in the presence of renal failure. Nitrofurantoin or nalidixic acid (p. 103) may also be used. A moderate degree of uraemia may be present which progresses little for months or years. This is especially so when hypertension is absent or minimal; in such cases salt and water depletion is often present due to failure of tubular reabsorption, and this aggravates the uraemia. Considerable benefit may result from an additional intake of salt as described under chronic glomerulonephritis (p. 599). When the renal infection is unilateral or if pyonephrosis has developed, nephrectomy may be indicated; rarely, high blood pressure may be cured by the removal of the diseased kidney.

Cystitis, Urethritis and Prostatitis

Reference has already been made to the possibility that some infections of the urinary tract may be confined to the urethra or bladder. In these the features of systemic illness are slight and the symptoms are those of frequency and dysuria. Scalding pain is felt in the urethra during micturition. Suprapubic pain of cystitis is felt before, during and a few moments after voiding urine. Although the bladder is empty there may be an intense desire to pass more urine due to spasm of its inflamed wall. Tenderness is often present in the suprapubic region, and the urine may have an unpleasant odour and appear cloudy. Pus cells, red cells and organisms may be seen on microscopical examination of the urine. Sometimes the urine is grossly blood-stained. Cystitis is particularly common in women and young girls, and the infection is usually due to *Esch. coli.*

In some patients with symptoms suggestive of urethritis and cystitis, no organism can be cultured from the urine. The term 'urethral syndrome' has been applied to this category of patients who are predominantly female. The cause of the symptoms is unknown although a variety of explanations, which include allergy, congestion of the urethra possibly related to sexual activity and infection of the urethral glands, have been put forward. In Reiter's disease urethritis may be associated with arthritis, conjunctivitis and sometimes diarrhoea (p. 771).

In acute prostatitis there may be considerable systemic disturbance. On digital examination of the rectum the prostatic gland is usually very tender.

Investigation. A possible predisposing cause for recurrent infections of the lower urinary tract should be sought though this is found in only a minority of cases. This may entail digital examination of the prostate, and gynaecological examination. Cystoscopy should be postponed until the acute condition has subsided. If there is reason to suppose that the kidneys are also involved, the examination should proceed with ureteric catheterisation, the collection of samples of urine from each kidney, and retrograde pyelography.

Treatment. Therapy is similar to that of acute pyelonephritis and is also discussed on page 603. In the majority of instances this is effective and there is no recurrence of the symptoms. In some patients, however, the clinical features of infection persist or recur.

The possible causes of failure to respond to treatment, or of relapse, are:

1. Infection with organisms resistant to the chemotherapeutic agent employed.
2. Tuberculosis, with or without secondary infection.
3. Continued infection from above, e.g. pyelonephritis associated with calculi.
4. Obstruction below the base of the bladder by:
    (*a*) prostatic hyperplasia, carcinoma of the prostate, or urethral stricture in the male;
    (*b*) chronic urethritis or stricture in the female.
5. Involvement of the bladder by:
    (*a*) malignant tumour arising in the bladder or in adjacent organs;
    (*b*) vesical calculus; foreign bodies may have been inserted into the bladder;
    (*c*) inflammation from adjacent structures, e.g. diverticular disease.

6. The presence of urethral caruncle, cystocele, urethrocele or cervicitis in the female or a meatal fissure in the male. The latter may be noted as a tender induration on examination of the meatus.

7. Paraplegia, in which urinary infection is frequent, persistent and often the ultimate cause of death.

Renal Tuberculosis

Tuberculosis of the kidney is invariably secondary to tuberculosis elsewhere in the body and occurs as a result of blood-borne infection. The initial lesion develops in the renal cortex and if untreated may ulcerate into the pelvis with consequent involvement of the bladder, epididymes, seminal vesicles and prostate. The disease tends to occur in young people and may manifest itself with recurrent haematuria and dysuria due to secondary involvement of the bladder. In addition the general features of tuberculosis, i.e. malaise, fever, lassitude and weight loss, may be present. Culture of the urine by ordinary methods may be sterile in spite of pyuria. The extent of the infection should be ascertained by cystoscopic examination, by pyelography, and by culture of the urine from both ureters. Chemotherapy should be given as for tuberculosis elsewhere in the body (p. 366). Partial or complete nephrectomy may be necessary in those in whom the disease has advanced to the stage of producing serious destruction of renal tissue with cavitation.

Renal Failure

(URAEMIA)

The term 'uraemia' has been used for more than a century to describe the clinical state which arises from renal failure. The retention of abnormal amounts of urea in the blood in renal disorders was amongst the early discoveries resulting from the application of biochemical methods to the elucidation of disease, and the symptoms of chronic renal failure were long attributed to it. The newer knowledge of renal physiology has shown that, as renal function becomes impaired, other complex biochemical changes occur and that these are probably more responsible for the clinical features of uraemia than the elevation of blood urea. These changes include disturbances in hydrogen ion concentration, abnormalities in water and electrolyte balance and the accumulation of many products of metabolism. In addition, renal failure is accompanied in the majority of cases by arterial hypertension, and this fact complicates still further the clinical picture.

Classification. Renal function may be impaired by disease affecting the renal parenchyma (renal uraemia), by extrarenal disorders such as acute circulatory failure (prerenal uraemia) or as a result of conditions in which there is obstruction to the outflow of urine (postrenal uraemia). Impairment of renal function results in renal failure which may be acute or chronic and of varying degrees of severity.

Acute Renal Failure may be due to a wide variety of conditions including acute proliferative glomerulonephritis, acute severe bilateral pyelonephritis, malignant hypertension, polyarteritis, renal involvement in systemic lupus erythematosus and eclampsia. In recent years, a condition in which primary vascular coagulation occurs and in which the glomeruli may be predominantly affected has also been described as causing acute renal failure (thrombocytopenic microangiopathy).

Acute renal failure occurs also in patients in whom initially there is no primary renal disease but in whom acute circulatory failure leads to sudden reduction in renal blood flow; this reduces the capacity of the kidneys to perform their functions. Thus prerenal uraemia occurs in states associated with water and salt depletion, shock, haemorrhage, etc. (p. 608). With appropriate treatment, this type of uraemia is commonly reversible and the prognosis is generally good. In a proportion of cases of prerenal uraemia, renal ischaemia may be so severe and prolonged as to produce damage to the renal parenchyma. When this affects only the tubules, the condition is called '*acute tubular necrosis*'. More rarely, but notably in cases of retroplacental haemorrhage occurring as a complication of pregnancy, the whole or a large part of the renal cortex is involved, the glomeruli as well as the tubules becoming necrotic. This is called *renal cortical necrosis.*

Chronic renal failure arises as a result of diseases which destroy renal tissue more slowly, e.g. progressive proliferative glomerulonephritis and the late stages of membranous glomerulonephritis (i.e. chronic glomerulonephritis), chronic

② ③

pyelonephritis, polycystic disease of the kidneys, hypertension, diabetic nephropathy, amyloid infiltration, tuberculosis and conditions causing hypercalcaemia.

For descriptive purposes, renal failure is conveniently subdivided into four categories based mainly upon the site of the lesion responsible:

1. Renal failure due to disease of the kidneys (renal uraemia).
2. Renal failure due to prerenal disease (prerenal uraemia).
3. Acute renal failure due to acute tubular necrosis.
4. Renal failure as a result of conditions in which there is obstruction of the renal tract resulting in impairment of renal function (postrenal uraemia).

I. Renal Failure due to Disease of the Kidney

(*Renal Uraemia*)

The clinical features and treatment of renal failure occurring as a result of glomerulonephritis are described on pages 597 and 599. The clinical features of renal failure occurring in the course of other chronic kidney diseases are essentially similar but are also those of the underlying disease.

II. Renal Failure due to Prerenal Disorder

(*Prerenal Uraemia*)

The performance of normal renal function is dependent upon the maintenance of an adequate renal circulation. The renal share of the cardiac output is normally about 25 per cent at rest. If the cardiac output falls the renal blood flow is disproportionately reduced. In this event, the glomerular filtration rate is reduced and oliguria results. While systemic hypotension often precedes prerenal uraemia, renal ischaemia may occur in its absence. Regional vasoconstriction is a means by which the blood pressure may be maintained in the face of oligaemia, and the success of this mechanism may deprive the kidneys of a large part of their blood supply. The urine that is formed is usually small in volume and the concentration of urea in the blood gradually rises. The more common causes of prerenal failure include:

1. *Loss of blood* from any cause including complications of pregnancy, trauma or gastrointestinal bleeding.
2. *Loss of plasma* as in burns and crushing injuries.
3. *Loss of fluid and salt.*
    - (*a*) *from the gut* in severe vomiting, diarrhoea, acute intestinal obstruction, paralytic ileus and fistulous drainage.
    - (*b*) *in the urine* in diabetic ketoacidosis and Addison's disease.
    - (*c*) *from the skin* in excessive sweating (heat stroke).
4. *General anaesthetics and surgical operations* causing hypotension or blood loss which may reduce renal blood flow and may precipitate renal failure in those whose blood volume is precariously balanced.

5. *Serious infection*, especially septicaemia from *Esch. coli*, may produce shock, and reduce renal blood flow.
6. *Acute cardiac failure* due to myocardial infarction or cardiac arrest.

These conditions should be treated by appropriate fluids given intravenously and by specific measures as indicated in the treatment of diabetic ketoacidosis, Addison's disease, infection, etc. Prompt and effective replacement of blood, water and salt is essential. In many cases vigorous treatment in the early stages prevents the occurrence of significant degrees of renal failure. If oliguria or anuria persists in spite of the return of the blood pressure to normal, acute tubular necrosis can be assumed to have occurred and should be treated accordingly.

III. Acute Renal Failure due to Acute Tubular Necrosis

Acute renal failure with tubular necrosis is a disease affecting both kidneys, characterised by anuria or oliguria with urine of low specific gravity and rapidly developing uraemia. Much of the earlier information about acute renal failure was obtained from studies of the 'crush' syndrome which occurred during the air raids of the Second World War.

Aetiology. Acute tubular necrosis occurs as a complication of various conditions which are associated with marked hypotension, arteriolar constriction and severe water and salt depletion, and which are listed above as causes of prerenal uraemia.

In other cases acute tubular necrosis develops unattended by any general circulatory disturbance. For example it occurs in some instances following incompatible blood transfusion or during acute haemolytic crises; it is also occasionally seen in patients with obstructive or hepatocellular jaundice, severe infection and septicaemia. Certain drugs are also capable of producing acute renal failure, e.g. sulphonamides and cephaloridine. Poisoning by substances, such as sodium chlorate, which produce renal parenchymal necrosis, may also be responsible.

Pathogenesis. Severe shock and water and salt depletion are accompanied by generalised vasoconstriction. Renal ischaemia results from the hypotension and afferent arteriolar vasoconstriction. If the ischaemia is severe and of sufficiently long duration, focal necrosis of the renal tubules occurs and may be aggravated by intravascular glomerular thrombosis.

The pathogenesis of renal tubular necrosis in cases unassociated with severe circulatory disturbances is not fully understood though it is believed that renal ischaemia may result from regional restriction in the renal blood flow with maintenance of the systemic blood pressure. In addition tubular casts of haemoglobin or plasma proteins and a rise in intrarenal pressure may contribute to the failure in some cases. In other cases, e.g. following sulphonamides or sodium chlorate, direct damage to the renal parenchyma from toxic or allergic reactions is responsible.

Clinical Features and Course. The clinical features of acute failure are those of the causal condition together with those of acute uraemia. Initially the urine volume is usually greatly reduced to between 200 and 500 ml/24 hour and this stage of the illness is called the *oliguric phase*. Any urine that is formed contains protein, casts and red and white blood cells. The specific gravity is usually about 1·010 early in the course of the disease, and this persists for several days or weeks. At first the patient may feel well, but after some days the features of uraemia appear. Initially these are anorexia, nausea and vomiting; apathy is followed by mental confusion and later muscular twitching, fits, drowsiness, coma, and bleeding episodes occur. At this stage the main dangers to life are (1) pulmonary oedema due to the injudicious administration of excessive amounts of fluid, (2) potassium intoxication due to the rise in the concentration of plasma potassium which is especially likely if there is haemolysis or massive soft tissue damage, (3) the occurrence of severe systemic infection to which such patients are susceptible, and (4) uraemia itself.

The oliguric phase of the disease usually lasts for one to three weeks and may include a period of anuria. If the patient does not succumb the daily volume of urine increases and rapidly may reach several litres. This is called the *diuretic phase* and coincides with healing of the renal tubules, reduction in intrarenal tension and resolution of intratubular casts and intraglomerular coagulation. During this phase there is uncontrolled water and sodium loss, and sometimes flaccid paralysis due to loss of potassium occurs in the absence of treatment. The concentration of blood urea ceases to rise and then gradually falls. Virtually complete recovery of renal function then takes place slowly over a period of three to six months.

Treatment

1. CAUSAL CONDITION. With a view to preventing or minimising the renal lesion, the underlying cause should be treated urgently and the appropriate solutions administered to replenish deficits.

2. THE OLIGURIC PHASE. Treatment during the oliguric phase has undergone many changes which have reflected the understanding of the disease process. Formerly treatment was based upon the crude assumption that the kidneys could be forced to secrete urine by giving large amounts of fluids intravenously or by the use of osmotic diuretics such as sodium sulphate or by surgical renal decapsulation undertaken to relieve intrarenal tension. There seems little doubt that the former high mortality was largely due to these procedures which have now been abandoned.

Clinical and pathological studies have shown that the ischaemic renal lesions are usually reversible provided the patient can be kept alive during the oliguric phase. Treatment is therefore designed to minimise the need for renal function until healing occurs and this can often be achieved by simple dietary restrictions.

Water and Electrolyte Balance. This is maintained by replacing the obligatory losses of water through the skin and lungs, estimated to be about 600 ml water/day, and by giving no electrolytes since none are being lost from the body. In febrile patients an extra allowance of water is required to replace the fluid lost through visible perspiration and a further small supplement equal to the volume of urine passed each day should be added. Should abnormal losses of fluid occur, as in diarrhoea, additional fluid will be required in appropriate amounts.

Protein and Calories. Dietary protein is restricted to about 20 g/day and attempts are made to suppress endogenous protein catabolism to a minimum by giving as many calories as possible as fat and carbohydrate. For this purpose a diet restricted in its protein and electrolyte content may be supplemented by a liquid glucose preparation such as Hycal. In the event of vomiting, oral treatment should be avoided and carbohydrate should be given in the form of 10 per cent fructose through a large peripheral vein.

In many patients in whom the acute renal failure is mild in degree and relatively short in duration this treatment prevents the blood urea from rising more than 20 mg per 100 ml per day, and the accumulation of potassium from protein catabolism is usually not sufficient to have serious consequences. If elevation of plasma potassium concentration should occur attempts should be made to reduce it by employing methods described on page 192; these include (1) the use of a sodium or calcium charged resin which removes potassium from the body, (2) giving 20 units of soluble insulin subcutaneously and an intravenous infusion of 50 g of glucose; and (3) controlling acidosis by intravenous administration of isotonic sodium bicarbonate.

Haemodialysis. In some patients, however, and especially in those suffering from severe infection or massive tissue damage, or in whom blood has become loculated in one of the tissue spaces, the rate of rise of blood urea and potassium is much more rapid and occurs in spite of the application of conservative methods; in these circumstances life may be threatened from acute renal failure within a few days. The patient should then be transferred to a centre equipped with the means for extracorporeal dialysis (artificial kidney). Daily haemodialyses may then be required over a period of several weeks before renal function returns. When this policy is adopted it is usually possible to be much more liberal regarding the intake of protein, fluid and calories. This is desirable from the point of view of encouraging repair of damaged or diseased tissues and is rendered possible by the daily correction of the composition of the blood and volume of body fluids achieved by the artificial kidney.

Peritoneal dialysis has been advocated as an alternative to haemodialysis. While this method has a place in the treatment of small children, it is a prolonged, uncomfortable, sometimes painful procedure fraught with complications.

3. RECOVERY OR DIURETIC PHASE. When diuresis commences the concentration of blood urea tends to remain constant for a few days and then begins to fall. When this occurs, a light diet, containing not more than 45 g protein per day and ample fruit, should be provided (Diet 13, p. 1003). Sufficient fluid must be given to replace the increased and uncontrolled loss of water in the urine. The fluid intake must be increased by the volume of the previous day's urinary output. Salt supplements are usually needed during the diuretic phase to compensate for increased urinary loss. On average about 3 g of sodium chloride and 2 g of sodium bicarbonate are needed for each litre of urine passed. The fruit usually compensates for the potassium loss, though in many cases a

supplement of potassium chloride by oral administration may also be required.

As the blood urea concentration returns to normal values and renal function improves a normal diet may be taken.

Patients with severe acute renal failure are seriously ill and require skilled nursing, preferably in single rooms designed to prevent airborne or contact infection. Great care must be exercised in the use of drugs which are normally excreted by the kidneys.

Prognosis. The high mortality accompanying acute renal failure with tubular necrosis has been greatly reduced by the measures described above. Prognosis depends upon the speed and efficiency with which the therapeutic measures are put into operation, the prompt recognition and effective treatment of complicating infection, and the nature and the severity of the condition precipitating the syndrome. In cases of uncomplicated acute renal failure, such as those due to simple haemorrhage, the mortality should now be less than 10 per cent even when haemodialysis is required. In severe renal failure complicated by infection or multiple injuries it is about 50 per cent.

IV. Renal Failure due to Postrenal Causes

(*Postrenal Uraemia*)

Renal failure may result from obstruction at any point in the urinary tract due to the causes given below. In the presence of two functioning kidneys ureteric obstruction causes uraemia only when it is bilateral.

Diagnosis. The diagnosis may be suggested by a history of previous urinary symptoms such as pain in the loins, haematuria, renal colic, nocturia or difficulty in micturition. However, in many instances the onset is clinically silent and the cause of the obstruction discovered only after appropriate investigations. In contrast to acute renal failure associated with tubular necrosis, anuria is common and the complete absence of urine suggests the need for cytoscopy, ureteral catheterisation and retrograde pyelography.

Treatment. Surgical treatment is required for all cases of renal failure due to postrenal obstruction. Uraemia may be severe, yet relief of the obstruction followed by a high fluid intake results in recovery of adequate renal function in many patients, provided that this treatment has not been delayed too long.

Obstruction of the Urinary Tract

Obstruction to the flow of urine from the kidney through the pelvis, ureter, bladder and urethra is a common disorder; it causes stasis and a rise in pressure within the urinary tract which predisposes to infection, stone formation and renal failure. Obstruction may occur at any level but is most often found at the pelvi-ureteric junction, in the ureter, at the neck of the bladder or in the urethra. Obstruction at the pelvi-ureteric junction causes hydronephrosis; obstruction of the ureter results in hydro-ureter and later hydronephrosis; obstruction of the bladder neck or urethra distends the bladder, causes hypertrophy of its muscle seen on cystoscopic examination as trabeculation, and hydro-ureter and hydronephrosis. If obstruction is unrelieved, slow progressive destruction of renal tissue occurs; superimposed infection may cause cystitis, ureteritis or pyonephrosis in which renal damage may become more rapid.

Aetiology. Obstruction may be due to an organic lesion in the lumen or in or around the wall of the urinary tract, or it may arise because of a congenital defect in the muscles of the pelvi-ureteric junction, ureter or bladder neck preventing the contraction wave and therefore the flow of urine. Organic causes include stone, blood clot, tumour, fibrosis following infection, or the precipitation of crystals due to sulphonamides. An aberrant renal artery, retroperitoneal fibrosis, accidental ligation at operation, carcinoma of the cervix, prostatic enlargement or phimosis may compress the lumen from outside.

Clinical Features. These vary with the cause and site of the lesion and in particular whether it is above or below the bladder. When the obstruction is supravesical, renal colic may occur, especially if the onset is sudden; more commonly the obstruction is gradual and an aching pain in the loins, sometimes aggravated by drinking, develops. Superimposed infection causes systemic manifestations with fever and dysuria. Haematuria is common.

When the obstruction is below the bladder, there is difficulty in micturition and the urinary stream is thin in calibre and poor in force. Complete urinary retention may occur with consequent distension of the bladder, which may be easily visible and palpable; either anuria or overflow incontinence ensues. In the latter event catheterisation reveals the presence of residual urine in the bladder after the patient has voided.

Treatment. In all cases the ultimate objective is to remove the source of obstruction; this is often possible, as in the case of a stone or prostatic hypertrophy. In the first instance it is necessary to relieve the obstruction in order to alleviate symptoms and preserve renal function. The action required varies with the nature of the underlying disease, but sometimes it may be dealt with initially and temporarily by draining the kidney, i.e. nephrostomy, the ureter, i.e. ureterostomy, or the bladder, i.e. suprapubic or urethral catheterisation. Antibiotics should be given if infection is severe but it is preferable to wait until the obstruction has been removed or relieved. When the hydronephrosis or pyonephrosis affects one kidney and this is severely damaged, nephrectomy is indicated. When obstruction affects both kidneys, appropriate treatment for renal failure should be given.

Renal and Vesical Calculi and Nephrocalcinosis

Aetiology. Urinary calculi have long presented fascinating aetiological problems which are still largely unsolved. Two or three centuries ago vesical calculus was so common in Britain that a respectable living could be made as a lithotomist, but the incidence is much lower at the present time for reasons that are not known. It is indeed surprising that renal and vesical calculi or nephrocalcinosis do not occur more frequently since some of the constituents of urine are present in a concentration in excess of their maximum solubility in water. It seems likely that urine contains certain substances, e.g. polypeptides, mucoproteins and citric acid, which, by forming complexes, keep otherwise insoluble salts in solution in the urine. Other authorities believe that the primary cause of urinary calculi is a pre-existing renal or vesical lesion which acts as a nidus on which urinary constituents precipitate. The following conditions are frequently associated with stone formation: (*a*) climate or occupation which necessitates living or working under conditions where excessive loss of water from sweating occurs, thus causing constituents to be precipitated because of their high concentration in the diminished volume of urine excreted; (*b*) urinary infection and stagnation; (*c*) conditions associated with hypercalciuria which increases the liability to the formation of stones consisting mainly of calcium phosphate and calcium oxalate. These include idiopathic hypercalciuria, prolonged immobilisation, hyperparathyroidism, Cushing's syndrome, sarcoidosis, multiple myeloma and vitamin D intoxication. Calcium phosphate stones tend to occur in alkaline urines and this may be an important factor determining their occurrence in idiopathic renal acidosis and in some patients with chronic pyelonephritis; (*d*) certain rare congenital abnormalities, e.g. cystinuria and primary hyperoxaluria, which may lead to the production of cystine or oxalate stones respectively; (*e*) conditions causing increased excretion of uric acid, e.g. gout and leukaemia; (*f*) dietary factors such as an excessive intake of milk or absorbable alkali.

Since the constituents of renal and vesical calculi are present in numerous articles of food it is not surprising that diet has been considered to be of aetiological importance. Many experimental investigations in animals have shown that by increasing the calcium content of the diet and reducing the intake of vitamin A, renal and vesical calculi can be produced regularly. Furthermore, the remarkable fall in the incidence of vesical calculi in children and young adults, which occurred in Britain in the nineteenth century, coincided with a marked improvement in the nutrition of the nation. Today, however, in prosperous countries the great majority of renal calculi occur in well nourished, healthy young men in whom the most careful investigations reveal no cause for stone formation.

Pathology. Urinary concretions vary greatly in size. There may be particles like sand anywhere in the urinary tract or large round stones in the bladder. Staghorn calculi fill the whole renal pelvis and branch into the calyces; they are usually associated with hydronephrosis and chronic pyelonephritis. Over 90 per cent of renal stones contain calcium but the nature of the salt varies with their origin. Deposits of calcium may also be present throughout the renal parenchyma, giving rise to nephrocalcinosis. This is especially liable to occur in cases of hyperparathyroidism, renal tubular acidosis, vitamin D intoxication, and in healed renal tuberculosis.

Clinical Features. These vary according to the size, shape and position of the stone, and the presence and nature of the underlying condition. Renal calculi or nephrocalcinosis may be present for many years and yet themselves give rise to no symptoms. While nephrocalcinosis never gives rise to pain, the most common complaint arising from renal calculi is an intermittent dull pain in the loin or back, increased by movement or a sudden jolt. Some abnormal constituents of the urine, e.g. red cells, protein or pus cells, can be found at one time or another in most cases.

Renal Colic. When a stone is small enough to enter the ureter and large enough to obstruct it, an attack of renal colic develops. The patient is suddenly aware of pain in the loin, which soon radiates round the flank to the groin and often into the testis or labia in the sensory distribution of the first lumbar root. The pain steadily increases in intensity to reach a maximum in a few minutes. The patient is restless, and generally tries, unsuccessfully, to obtain relief by assuming various positions, both lying and sitting, and by pacing about the room. There is pallor, sweating, and often vomiting, and the patient may groan in agony. Frequency and haematuria may occur. Without treatment the intense pain usually subsides within two hours but may continue unabated for several hours or some days. In many cases the pain is constant during the attack, though slight fluctuations in severity may occur. Contrary to what is often believed, it is rare for attacks to consist of intermittent severe pains, coming and going every few minutes for some hours.

Diagnosis. When renal colic occurs the diagnosis is usually easily made as it can be established by the history and by the finding of red cells in the urine. All patients suspected of having renal calculus, including those with renal colic, should have a radiological examination of the urinary tract, including retrograde pyelography in some instances. If there is doubt about the cause of the abdominal pain, an intravenous pyelogram during the attack may be helpful. When the pain is due to a stone in the ureter, the radiograph shows a dense renal shadow with delay in the appearance of the dye in the renal pelvis. Appropriate investigations should be undertaken to discover the presence of any underlying condition which might be responsible for the development of renal calcification or lithiasis.

Prognosis. This varies greatly depending on the underlying cause and on whether the patient passes the stone in the urine or whether it continues to obstruct the ureter. In the latter case, if the stone is not removed surgically, hydronephrosis and pyelonephritis are likely to develop in time.

Treatment and Prevention. The immediate treatment of renal pain or renal colic is rest in bed, the application of warmth to the seat of pain, and the administration of analgesic drugs, e.g. pethidine (100 mg) or morphine (15-30 mg), and antispasmodic drugs, e.g. atropine sulphate (0·8 or 1·2 mg). These should be given intramuscularly and may be repeated within two hours. Attempts to dissolve calculi in the kidneys have not been successful. Stones in the renal pelvis and urinary bladder must be removed surgically. Stones in the ureter usually pass naturally if left alone and surgical removal is apt to be followed by stricture and its complications. When, however, pain persists or frequent bounts of pain become intolerable, the insertion of a ureteric catheter is often followed by the passage of the stone. Urgent surgical intervention is necessary in the event of anuria. It is also required if the stone has not moved for some months and hydronephrosis is developing or there is continuing infection in the urinary tract. A stone larger than 1 cm in diameter generally requires surgical removal.

Suitable medical or surgical measures should be instituted for the correction of any primary cause of renal lithiasis that may have been discovered.

Dietary restrictions prescribed with the object of preventing the formation of stones, are useful in the case of idiopathic hypercalciuria, with recurrent oxalate stones and in persons who have passed several uric acid stones. In idiopathic hypercalciuria a diet low in calcium, by reducing the intake of milk and cheese, is advisable. When dietary restriction is impracticable, bendrofluazide in a dose of 5 mg/day reduces urinary calcium excretion by about 30 per cent. The mechanism of this action is unknown but is probably renal. An alternative or supplementary treatment is the use of cellulose phosphate (5 g t.i.d.) which binds calcium in the diet and prevents absorption. In recurrent oxalate stones the elimination from the diet of articles which have a very high content of oxalate, such as rhubarb or spinach, may be worthy of trial. The avoidance of liver, kidney, sweetbreads, fish roe, sardines and sprats, articles with a very high purine content, is advisable in persons who have passed several uric acid or urate stones, as may occur in gout or in patients with leukaemia. This treatment may also be supplemented by the use of allopurinol (p. 785). Since the distribution of phosphorus occurs so widely in foodstuffs, dietary restriction for the treatment of phosphate calculi is unlikely to be of any value. Phosphatic calculi are found only in alkaline urine, hence acidifying the urine by administering ammonium chloride daily may be effective. In contrast, cystine and urate stones may be prevented or sometimes dissolved by making the urine persistently alkaline, especially if combined with a high output of urine.

Lastly, the most important therapeutic and prophylactic measure for all forms of stones is the provision of an adequate fluid intake which assists in preventing deposition of crystalloids in the renal tissue. A daily output of urine of at least 3 *l* is advisable; hence the intake of fluid should be approximately 4 *l* daily. If the climate or the patient's occupation causes much sweating the fluid intake requires to be greatly increased.

Renal Hypertension and Unilateral Renal Disease

The frequent occurrence of hypertension in patients with bilateral renal disease has been recognised for many years. Unilateral renal disease is a rare cause of hypertension but one which may be remedied by nephrectomy. It is now recognised that surgical treatment is likely to be of value only when the renal lesion causes under-perfusion of the kidney (renal ischaemia).

In the elderly, the most frequent causes of unilateral renal ischaemia is stenosis due to atheromatous plaques in the main renal artery. In the young, fibromuscular dysplasia, a rare congenital defect, may cause narrowing of the renal artery. At any age chronic pyelonephritis may also be responsible for unilateral renal ischaemia as a result of endarteritis in the intrarenal arteries. The presence of these lesions should be suspected if there is a history suggestive of pyelonephritis, in malignant hypertension, or if a systolic murmur is heard over the kidney. Intravenous pyelography may show features of chronic pyelonephritis or renal ischaemia—the affected kidney is reduced in size, there is contraction of the calyces, delayed appearance and increased concentration of the contrast medium within the pelvis. The radiohippuran renogram shows evidence of disparity in function between the two sides. In a proportion of cases the ischaemia gives rise to secondary aldosteronism and potassium depletion.

Nephrectomy or surgical reconstruction of the renal artery should be considered in young hypertensive patients in whom these investigations and the estimation of function in each kidney have demonstrated unilateral ischaemic disease. Over the age of 40 years renal artery stenosis may be a secondary feature of the hypertension rather than its primary cause, and treatment with hypotensive drugs is the therapy of choice in the majority of patients. Spironolactone may be necessary when the features of secondary aldosteronism are severe; it also exerts a useful hypotensive effect in such circumstances.

Polycystic Disease of the Kidneys

Polycystic disease is a genetically determined abnormality of renal structure and is often associated with other congenital abnormalities, e.g. cystic liver. There are two modes of inheritance. The commoner or adult type is inherited as an autosomal dominant trait. The infantile form is very rare and is inherited as an autosomal recessive; it is usually fatal within the first year of life.

The adult condition may be found during infancy, but symptoms often do not develop until adult life. Both kidneys are affected, are several times the normal size, and consist of masses of cysts with a variable amount of renal parenchyma which often shows extensive fibrosis and arteriolosclerosis.

The clinical features include pain in the renal angles, haematuria, uraemia and usually a slowly developing arterial hypertension. Often one or both of the kidneys can be palpated and the surface may be nodular. In addition to polycystic disease, other diseases in which the kidneys may be palpable are hydro- or pyonephrosis, solitary cyst, renal carcinoma and other tumours. It should be remembered, however, that in some normal people all of the right kidney, and occasionally the lower pole of the left kidney may be felt on clinical examination. This is particularly true in slim women. On the other hand, pathologically enlarged kidneys are not always palpable. When a kidney can be felt, as in polycystic disease, it may be possible to appreciate departures from the normal size, smooth surface and firm consistency.

In course, prognosis and treatment, polycystic disease resembles chronic glomerulonephritis, and death occurs in middle age from uraemia, cerebrovascular accident or cardiac failure.

Tumours of Kidney and Urinary Tract

Renal Carcinoma

This is the most common tumour of the kidney. It was formerly called a hypernephroma on the mistaken view that it arose from adrenal rest tissue within the kidney. Haematuria is the most frequent presenting feature and blood clots may give rise to renal colic. Sometimes the tumour causes vague abdominal pain and it may also be responsible for long continued fever. Occasionally patients present first with symptoms arising from metastatic foci in the lungs, liver or bones. On rare occasions polycythaemia occurs, and this is believed to be due to excessive production of erythropoietin (p. 742). The diagnosis may be suspected from the history or the tumour may be palpable. Radiological investigation is usually essential, and aortography may distinguish the filling defect from that due to simple cyst which is avascular. Early surgical treatment affords the only prospect of cure.

Nephroblastoma (Wilm's Tumour)

This is the second most common malignant tumour of the kidney and presents in the first decade, and often the first year of life. The tumour is radiosensitive and the best hope of cure is early diagnosis and surgical removal followed by radiotherapy.

Tumours of Renal Pelvis, Ureter, Bladder and Prostate Gland

Tumours of the renal pelvis, ureter and bladder are histologically similar and are almost always transitional cell carcinomata. They tend to spread locally by direct invasion but also by implantation to other parts of the urinary tract. While some are benign, e.g. papillomata, all urinary tract tumours are liable to recur even after apparently adequate treatment. The bladder is by far the most common site and epidemiological studies have shown that it is particularly likely to develop in patients who work in industries where exposure to analine is likely such as dyeing and printing. Haematuria as a sole presenting symptom is almost universal. Features due to obstruction to the urinary tract also occur and symptoms of urinary tract infection may be superimposed. Diagnosis is made by cystoscopy, biopsy and radiography. Bladder tumours are treated by diathermy or radiotherapy. Cystectomy with transplantation of the ureters to colon or skin may be necessary.

Prostatic carcinoma usually presents with symptoms of urethral obstruction similar to those of benign prostatic hypertrophy. On digital examination of the rectum the prostate is felt to be very hard and the median furrow may be obliterated. Spread through the capsule and metastases in bone occur and are often associated with a rise in the serum acid phosphatase. Both the primary growth and metastases can be controlled with oestrogens, e.g. dienoestrol. Gynaecomastia is a troublesome side-effect. In some cases orchidectomy may also be necessary.

Testicular Tumours

Tumours of the testes are uncommon but are usually malignant, sometimes spreading to the lungs at an early stage. A seminoma presents as a painless and often rapid uniform enlargement of the testes while a teratoma causes nodular enlargement. Some teratomas produce gonadotrophic hormones and cause gynaecomastia. Treatment is by orchidectomy and radiotherapy. Teratomas are more radio-resistant and the prognosis is poorer.

Benign Enlargement of the Prostate Gland

This is sometimes referred to as benign hypertrophy. Its cause is unknown but it may be associated with a fall in androgen secretion. It is most commonly found in men over 60 years. Histologically the inner zone of the gland undergoes hyperplasia and hypertrophy and there is an increase in the fibromuscular stroma. The enlarged prostate obstructs the outflow of urine from the bladder by compressing, displacing, distorting and elongating the prostatic urethra with the effects on bladder and renal function referred to on page 613.

The clinical features are those of progressive obstruction to urinary flow. Acute urinary retention may arise if the gland suddenly increases in size because of superimposed infection or congestion, or when cardiac failure develops in the elderly. Then the patient has a sudden desire to micturate but is unable to do so, the bladder becomes tense and is tender. More chronic retention may pass unnoticed for some time but there is a gradual increase in the volume of urine which remains in the bladder after micturition. Haematuria and bleeding from the urethra may also occur and may be the presenting symptom. On rectal examination the prostate may feel large, elastic and is uniform in consistency; however, when the median lobe alone is affected, the prostate feels normal and the condition can be recognised only by cystoscopy.

Prostatectomy is the only effective treatment and the important decision is when to operate. Acute retention should be relieved by catheterisation and drainage; sometimes this reduces congestion and the ability to pass urine spontaneously can be regained. If this does not occur, operation should be carried out in a few days.

PREVENTION OF DISEASES OF THE KIDNEY AND THE URINARY TRACT

In recent years the incidence of acute proliferative glomerulonephritis has considerably diminished. This is probably due to a combination of factors which include the wider use of antibiotics in the treatment of streptococcal infections and improved social conditions. However, since acute glomerulonephritis may follow a slight throat infection for which the patient does not attend a doctor, prophylactic chemotherapy is not always practicable. In any case neither chemotherapy for tonsillitis nor tonsillectomy necessarily prevents the subsequent development of acute nephritis. Accordingly there is little hope of preventing this complication until more is known of the unusual reaction to infection which occurs in acute nephritis. However, in the event of an epidemic of streptococcal infection with a nephritogenic strain occurring in a closed community, the prophylactic administration of penicillin should be given to all contacts and to streptococcal carriers.

There is no known method of preventing minimal lesion or membranous glomerulonephritis. The liability to develop diabetic nephropathy may be reduced by careful control of the diabetes.

With regard to prevention of infections of the urinary tract, the early diagnosis of the cause and the complete elimination of the infection are very important factors in preventing the development of chronic pyelonephritis. This is of particular importance in the asymptomatic urinary tract infection in pregnancy. All pregnant women should be screened with routine culture of midstream specimens of urine. Appropriate antibacterial treatment should be given to those in whom organisms are found in the urine. Reference to the section on renal calculi and nephrocalcinosis will indicate various prophylactic measures of value in these conditions. Acute renal failure may be prevented in some cases by prompt action to restore the blood pressure in hypotension. The incidence of polycystic disease might be reduced by appropriate genetic advice. The frequency of carcinoma of the urinary bladder could be reduced by precautions in the gas, dye and rubber industries, and possibly by giving up cigar smoking.

A large, long-continued consumption of phenacetin can cause renal damage, in particular necrosis of the renal papillae, terminating in renal failure. The primary effect may be on the renal arterioles leading to ischaemia. Phenacetin should not be given to patients with chronic renal disease or pyelonephritis, and should not be prescribed on a long-term basis, for example to patients with arthritis. Other drugs such as certain antibiotics (p. 600) and possibly the prolonged use of other analgesics may also cause renal damage. Many drugs must be used with great caution in the presence of renal failure.

Finally, the adequate and early investigation of a symptom such as haematuria frequently leads to the discovery of the causal condition at a stage amenable to radical cure.

J. S. Robson.

Further reading:

Black, D. A. K. (1973). *Renal Disease*, 4th ed. Oxford: Blackwell.

Macleod, J. (1973). *Clinical Examination*, 3rd ed. Edinburgh and London: Churchill Livingstone.—For further information about examination of the kidneys and the urine.

Passmore, R. & Robson, J. S. (1971). *Companion to Medical Studies*, vol. 1, p. 33.1. Oxford: Blackwell.

Passmore, R. & Robson, J. S. (1973). *Companion to Medical Studies*, vol. 2, p. 11.1. Oxford: Blackwell.

Passmore, R. & Robson, J. S. (1974). *Companion to Medical Studies*, vol. 3, p. 22.1. Oxford: Blackwell.

de Wardener, H. E. (1973). *The Kidney*, 4th ed. Edinburgh and London: Churchill Livingstone.

Diseases of the Endocrine System

The advances that have been achieved in the technology of hormone assay have resulted in a better understanding of clinical endocrinology in physiological terms. The isolation and synthesis of hormones or biologically active analogues have made many endocrine diseases eminently amenable to treatment. Until recently many hormone assays were confined to research laboratories but with improved techniques and understanding of their clinical application an increasing range of assays is becoming available to the clinician. Among the methods in use are radioimmunoassay, competitive protein binding and fluorimetry, and, at the time of writing, cytochemical techniques appear likely to provide a new order of sensitivity in the measurement of certain pituitary hormones. In order to take full advantage of such improvements in laboratory aspects of endocrinology the clinician, while clearly having to maintain his clinical acumen, must also be familiar with the investigative aspects of the subject. This is discussed in some detail in this chapter.

The application of the science of immunology to endocrinology has been responsible for many of the advances, notably radioimmunoassay of all the hormones produced by the anterior pituitary gland and of many of the hormones produced by its target glands, thyroid, adrenal, testis and ovary. In addition, the study of immunology has thrown much light on the possible pathogenesis of many endocrine diseases in terms of autoimmunity, including certain of the thyroid diseases, a form of adrenal insufficiency and of parathyroid insufficiency, certain types of gonadal failure and possibly some aspects of diabetes mellitus.

Among the advances in clinical endocrinology has been the recognition of a form of thyrotoxicosis which is due to the excessive secretion of triiodothyronine alone. The understanding of the role of the hypothalamus in disease has been consequent upon the identification and synthesis of hypothalamic releasing and inhibitory hormones which affect the pituitary. It is also now known that certain non-endocrine tumours synthesise and secrete trophic hormones such as ACTH or biologically active analogues of these.

While the metabolic aspects of the commonest of the endocrine diseases, diabetes mellitus and thyrotoxicosis, can be readily controlled, some of the complications of these conditions remain poorly understood, particularly angiopathy in diabetes mellitus and exophthalmos in thyrotoxicosis.

Endocrinology also permeates many other clinical disciplines, not only because disordered function of the endocrine glands may affect every organ in the body, but because corticosteroids are extensively used for the control of inflammation and adverse immune reactions in a variety of serious disorders. When used in pharmacological doses for these purposes there may be both beneficial and adverse effects because the anti-inflammatory action of the corticosteroids cannot be separated from their hormonal activity.

Among the benefits which will accrue if clinicians make full use of new knowledge in endocrinology is that disease will be more readily detected in its early stages and unnecessary morbidity avoided.

THE HYPOTHALAMUS AND THE PITUITARY GLAND

Anatomy and Physiology

The pituitary gland is enclosed in the sella turcica, bridged over by the diaphragma sellae, with the sphenoidal air sinuses below, and the optic chiasma in the subarachnoid space above. The gland is composed of two lobes, anterior and posterior, and is connected to the hypothalamus by the infundibular stalk carrying nerve fibres to the posterior lobe, and the portal vessels from the median eminence of the hypothalamus to the anterior lobe of the pituitary gland.

The anterior lobe consists of three main histological types of cell, chromophobe, eosinophil and basophil. It affects growth, thyroid activity, sexual function, lactation and water, carbohydrate, protein and fat metabolism by regulating the secretions of the other endocrine glands.

The posterior lobe (pars nervosa or neurohypophysis) contains neuroglial fibres which emanate from the supra-optic and paraventricular nuclei of the hypothalamus.

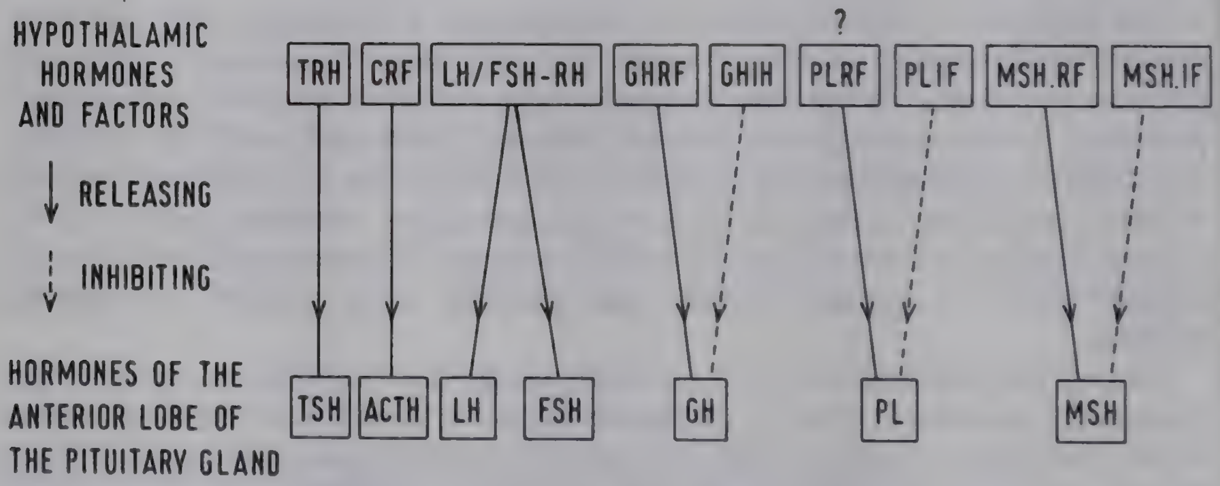

HYPOTHALAMIC HORMONES AND FACTORS
RELEASING
INHIBITING
HORMONES OF THE ANTERIOR LOBE OF THE PITUITARY GLAND
?
TRH
CRF
LH/FSH-RH
GHRF
GHIH
PLRF
PLIF
MSH.RF
MSH.IF
TSH
ACTH
LH
FSH
GH
PL
MSH

FIG. 78

The relationship between the hypothalamus and the anterior lobe of the pituitary gland. Hypothalamic releasing (R) and inhibiting (I) activities are described as hormones (H) when they have been chemically identified and synthesised, and as factors (F) while their recognition still depends upon biological activity only, as determined in animal studies.

Hormones of the Anterior Lobe. Secretion of each of the seven hormones formed by the anterior lobe of the pituitary gland is influenced by a stimulus provided by the hypothalamus, either in the form of a releasing hormone or factor, or by an inhibitor which suppresses secretion (Fig. 78).

The secretion of the hypothalamic factors in turn is dependent upon a wide variety of stimuli of nervous, metabolic, physical or hormonal origin, in particular from the appropriate target organs of the pituitary hormones, the thyroid gland, the adrenal cortex and the gonads. The secretion of corticotrophin, and presumably of the hypothalamic corticotrophin releasing factor (CRF), in addition is time dependent, being most active in the morning, and least in the evening, except when this physiological diurnal (circadian; nyctohemeral) rhythm is overridden by other stimuli, particularly emotional or physical stresses.

The thyrotrophin releasing hormone (TRH) formed in the hypothalamus, like the other hypothalamic releasing or inhibiting factors, passes through the portal system of vessels connecting the median eminence of the hypothalamus to the anterior lobe of the pituitary gland, where it promotes the secretion of the thyroid stimulating hormone (TSH). The luteinising hormone and follicle stimulating releasing hormone (LH/FSH-RH) acts on the pituitary to release both LH and FSH. In the male it is known as interstitial cell stimulating hormone (ICSH). Growth hormone (GH) however is controlled by a dual system, namely growth hormone releasing factor (GHRF) and an inhibitory hormone (GHIH). Prolactin is under the control of an inhibitory factor (PLIF) and may also be influenced by a releasing factor (PLRF), but this is less certain; likewise the melanocyte stimulating hormones (α and β MSH) with their releasing factor (MSHRF) and inhibitory factor (MSHIF). It is noteworthy that the pituitary hormones with target glands (TSH, ACTH, FSH and LH) appear to be controlled by hypothalamic releasing hormones alone. By contrast, the pituitary hormones without target glands (GH, PL and MSH) may have a dual control mechanism from the hypothalamus, namely a releasing factor, opposed by a specific inhibitory factor.

Some of these hypothalamic hormones (TRH, LHRH, GHIH) have already been synthesised and are being used in the clinical investigation of disorders of the hypothalamo-pituitary system and its target glands.

Hormones of the Neurohypophysis. The neurohypophysis secretes two hormones, vasopressin and oxytocin. The principal action of vasopressin is to increase the reabsorption of water by the renal tubules, so that the osmolality of the blood is maintained. Because of this action it is also known as the antidiuretic hormone (ADH).

Oxytocin induces contraction of the parturient uterus and is widely used in obstetrics for this purpose.

Diagnosis of Disordered Pituitary Function

The development in recent years of radioimmunoassay has provided a new dimension of sensitivity applicable particularly to the protein and peptide hormones of the pituitary gland. All can now be measured in body fluids, though some of the techniques are still restricted largely to research laboratories. In addition, three hypothalamic hormones, namely TRH, LHRH and GHIH, have been synthesised and can be used to stimulate or inhibit the release of the appropriate pituitary hormone. Furthermore, the methods of assay for the hormones produced by the target glands of the pituitary are more reliable and more readily available than previously. Thus it is now possible to assess very fully and specifically the functional activity and the secretory capacity of the pituitary gland and its target organs. Several pituitary hormones, namely TSH, ACTH, GH, and gonadotrophins are available in suitable forms for the investigation and treatment of endocrine disorder, and are particularly valuable in distinguishing between primary insufficiency of the adrenal cortex, the thyroid gland and the gonads, and secondary failure due to reduced or absent secretion of one or more pituitary trophic hormones.

The methods used in applying assay procedures to the diagnosis of pituitary disease must always be discussed in advance with the laboratory staff responsible for the hormone assays, so that the overall procedure is standardised. For example, in assessing increased production of growth hormone (acromegaly, p. 626), a standard glucose tolerance test is performed with radioimmunoassay of growth hormone at half-hourly intervals along with measurements of blood sugar. Under physiological conditions growth hormone secretion is promptly suppressed by a rise in the blood sugar level, while there is no significant suppression in patients with pituitary tumours secreting growth hormone.

In assessing impaired secretion of growth hormone insulin hypoglycaemia may be used (p. 664); this has the added advantage of stimulating the pituitary to secrete ACTH which can be monitored by estimating plasma 11-OH corticosteroids and also prolactin. In children more convenient screening tests are the rebound increase of plasma growth hormone at two and a half to three hours after oral glucose or the response in GH to Bovril, exercise or oral arginine.

In the case of the thyroid gland, TRH can be given intravenously and the pituitary response assessed by measuring the serum TSH concentration at pre-arranged intervals afterwards. LHRH can be given intravenously and the plasma LH and FSH measured at intervals thereafter. The precise timing of the samples to be taken, the number of samples, usually several, the separation of plasma or serum from the red cells, and the conditions of storage are also critical factors in making a reliable assessment of the function of the pituitary gland.

Clinical Manifestations of Pituitary Disease

The clinical features of pituitary disease vary, depending on the type of lesion in the pituitary gland, and on whether both lobes are involved or only one. Destruction of the gland in part or in its entirety will be followed by hypopituitarism (p. 627). Enlarging tumours of the gland may present with signs attributable to increased output of hormones or, more commonly, to failure of secretion. Some tumours secreting hormones compress the remaining pituitary tissue, so that there may be failure of some functions of the gland in the presence of an excess of other functions. Failure of function may be progressive and sequential; secretion of gonadotrophins usually declines first, followed by GH, ACTH and finally TSH.

Tumours of the Pituitary Gland

About 80 per cent of pituitary tumours are chromophobe adenomas, and unless of mixed type, are non-secretory, and associated with hypopituitarism. Eosinophil adenomas, associated with excess secretion of growth hormone, come under clinical observation with acromegaly (p. 626), or rarely, in the adolescent, as giantism (p. 626). Basophil adenomas secrete corticotrophin and

MSH, and may present as Cushing's disease (p. 656). These basophil tumours are usually too small to produce local pressure effects, except in cases of long standing, or after bilateral adrenalectomy several years earlier (Nelson's syndrome, p. 657).

Craniopharyngiomas are tumours or cysts developing in cell rests of Rathke's pouch, and may be located within the sella turcica, or commonly in the suprasellar space, where they frequently calcify. In either situation their clinical presentation is likely to be due to pressure on one or both lobes of the pituitary gland, on the stalk, on the hypothalamus, or on the visual pathways. Primary carcinoma of the pituitary gland is particularly rare, but a metastatic tumour from a primary in the breast, lung, kidney or elsewhere may occur. Other tumours, for example pinealoma, ependymoma or meningioma, may occasionally be associated with some disturbance of pituitary function.

Clinical Features due to the Site and Size of the Tumour. Headache is the most constant but least specific symptom. Involvement of an optic nerve, the optic chiasma, or an optic tract may lead to impaired visual fields. The patient occasionally notices a visual field defect, but, more commonly, examination of the visual fields by confrontation or by perimetry will be required to identify the likely point of interference within the visual pathway (Fig. 94, p. 812), bitemporal hemianopia being the characteristic lesion. Optic atrophy may be apparent on ophthalmoscopy. Diplopia and strabismus may follow pressure on the third, fourth and sixth cranial nerves.

Enlargement of the sella turcica and erosion of the clinoid processes may be detected on radiological examination, or suprasellar calcification in a craniopharyngioma. A 'double floor' may be apparent on tomography of the sella if the tumour is expanding downwards. Air encephalography may be particularly helpful in delineating tumours which have spread beyond the sella turcica. Some tumours expand sufficiently to interfere with vasopressin secretion and so cause diabetes insipidus. Tumours which expand upwards to impinge on the hypothalamus may be associated with disturbances of sleep and of appetite. Obesity arising in this way is part of the rare Frohlich's syndrome.

Treatment of Pituitary Tumours. Two main considerations determine whether surgical treatment is required. If there is evidence of pressure on the visual pathways, for example a visual field defect, surgical treatment is appropriate. Secondly, if hyperfunction, as judged by suitable assays, is sufficiently severe to affect the patient's welfare and prognosis, then treatment aimed at destroying the tumour or its capacity to secrete should be considered. Relief of pressure may be achieved by operation, either through a transfrontal craniotomy, or from below by a trans-sphenoidal approach.

Adequate suppression of secretory capacity may be achieved without open operation using either radiotherapy applied externally, or internally by placing a source of radiation, for example ^{90}Yttrium in pellet form, within the pituitary gland. This latter technique should be undertaken only in centres equipped for stereotactic intracranial surgery. Replacement therapy (p. 629) is likely to be required during and after treatment in this way.

Syndromes due to Anterior Pituitary Hypersecretion

Eosinophil Cells. Hypersecretion of growth hormone may develop very rarely before the epiphyses have united, to produce *giantism*. Much more frequently it occurs in adult life, after union of the epiphyses, and the condition is described as *acromegaly* (large extremities). If hypersecretion begins in adolescence and persists into adult life, giantism and acromegaly may be associated. Acromegaly is characterised by an increase in the size of the bones and soft tissues of the hands, feet, supraorbital ridges, sinuses and the lower jaw. The skin becomes thick and coarse; the subcutaneous tissues increase in depth, while enlargement of the tongue, lips and ears may be conspicuous. The viscera, for example the heart, thyroid and liver, enlarge. Carbohydrate tolerance is reduced in about 30 per cent of cases to the extent that diabetes mellitus develops. As the disease progresses, the patient often develops a kyphosis and muscular weakness. Hypertension is a common complication. The disease tends to progress slowly over several years, but patients are frequently seen with certain features of acromegaly in whom the progress of the condition has apparently been arrested, or a phase of hyperpituitarism may pass into hypopituitarism. Sensitive radioimmunological methods of assaying growth hormone in blood now make it possible to assess with precision the activity of these tumours as well as the results of treatment.

Basophil Cells. Hypersecretion by these cells or possibly by chromophobes leads to *Cushing's disease* (p. 656).

Syndromes due to Anterior Pituitary Hyposecretion

Pituitary Dwarfism and Infantilism

In children hyposecretion causes dwarfism and pituitary infantilism. The term 'dwarfism' means that growth is retarded; 'infantilism' implies that sexual development is subnormal for the individual's age, though it is also used to indicate retention of infantile as opposed to adult proportions of the head, limbs and trunk.

While pituitary tumours are an uncommon cause of dwarfism, delayed growth and development is characteristic of most pituitary tumours in children. In addition to requiring full assessment by assays of pituitary hormones, for example TSH, GH, ACTH and gonadotrophins, or if the techniques are not available, by the assay of target organ hormones, it is essential that accurate records be kept of the child's height, weight and bone age. Radiographs of the left hand and wrist taken at intervals of one year can be compared with the standard atlas prepared by Greulich and Pyle, so that the progress of bone development is assessed. Records of progress have become particularly important since it is now possible to obtain supplies of growth hormone in Britain from the Medical Research Council for the treatment of children in whom the need for this has been adequately established. Intramuscular injections are given twice weekly for several years according to the response. Height and weight should be recorded on a Tanner and Whitehouse chart which can be purchased from Creaseys Ltd, Bull Plain, Hertford, England.

DIFFERENTIAL DIAGNOSIS OF DWARFISM

Growth may be delayed or impaired for many reasons. Tallness and shortness of stature have genetic components. One form of dwarfism is Turner's syndrome in which there is absence of a second X chromosome (p. 11). Premature birth may be associated with persistent stunting of growth; this also occurs in anoxic forms of congenital heart disease, in chronic liver disease, in many chronic infections, and in persistent undernutrition for any reason. A number of other specific conditions commonly associated with dwarfism are described briefly.

(*a*) INFANTILISM DUE TO MALABSORPTION (p. 493). This disability is associated with steatorrhoea and defective absorption, especially of fat, minerals and vitamins. Dwarfs of this type are usually larger than the pituitary type; they may be further distinguished by a prominent abdomen due to intestinal distension, and by a history of the passage of pale, bulky, offensive stools. Fibrocystic disease of the pancreas may simulate malabsorption due to gluten induced enteropathy.

(*b*) RICKETS (p. 137). A defective diet or malabsorption may be responsible; kyphosis, pigeon-chest deformity and leg-bowing are common sequelae.

(*c*) ACHONDROPLASIA. This hereditary disorder of endochondral ossification is characterised by failure of the long bones of the arms and legs to grow properly, while the trunk and head develop normally. Dwarfs of this type are sexually and intellectually normal and frequently used to appear in circuses.

(*d*) RENAL DWARFISM. Renal failure arising in early childhood may be caused by 'achalasia' at the outlet of the bladder, which produces back-pressure and hydronephrosis, or it may be due to congenital cystic disease, congenital hypoplasia of the kidneys or, most commonly, chronic nephritis. Many of the characteristic features of renal failure may be found, for example hypertension, a raised blood urea and changes in the fundus of the eye. In some cases hereditary defects of renal tubular function may be responsible.

(*e*) CRETINISM AND JUVENILE HYPOTHYROIDISM. If these conditions are not recognised and treated early in childhood, stunting of growth will occur (p. 644).

Hypopituitarism

Aetiology. At one time destruction of the anterior lobe of the hypophysis was commonly due to infarction and this was often a sequel to post-partum haemorrhage (Sheehan's syndrome). Improvements in obstetrical care have greatly reduced the incidence of this accident and the disorder is now most commonly due to a chromophobe adenoma. Other causes include non-secretory tumours, a fractured skull, infection, granulomata (syphilis, sarcoidosis) and the presence of simple cysts. In some, an 'empty sella' may be due to a previous granuloma. Idiopathic cases are probably the result of failure of the hypothalamus to secrete the appropriate releasing hormones. Surgical treatment of tumours of the gland is often followed by a degree of hypopituitarism calling for replacement therapy, and complete hypophysectomy is sometimes performed in the treatment of malignant disease, for example carcinoma of the breast.

Clinical Features. In Sheehan's syndrome, a history is usually obtained that several years before the onset of the presenting illness, the patient had a difficult confinement with haemorrhage and a need for blood transfusion. Lactation failed or was never established, amenorrhoea persisted indefinitely and other changes attributable to the absence of the trophic hormones gradually made their appearance. Some of the features of hypothyroidism are usually present, but myxoedema is seldom prominent. Loss of weight is uncharacteristic and when present is often due to some other disease. Absent or scanty axillary and pubic hair are characteristic findings. Symptoms of adrenal insufficiency and a low blood pressure may be noted, but the changes in serum electrolytes found in severe adrenal insufficiency do not occur in hypopituitarism. This is probably because aldosterone continues to be secreted by the glomerulosa layer of the adrenal cortex, since this function is largely independent of corticotrophin. Cortisol production, however, falls to a minimum because the essential corticotrophic stimulus from the pituitary gland is absent or inadequate. In contrast to the pigmentation of the skin in Addison's disease (p. 660) a striking degree of pallor is often one of the signs suggesting hypopituitarism. Although a mild degree of normochromic anaemia is usually present, this is insufficient to explain the pallor of the skin. Capillary vasoconstriction and the absence of melanin together account for this arresting sign.

COMA IN HYPOPITUITARISM. Patients with hypopituitarism are peculiarly liable to go into coma if inadequately treated. While the onset of coma may occur for no apparent reason, it usually follows some mild infection or injury, in the same way that an Addisonian crisis may follow some relatively trivial stress (p. 661). The coma may be due to one or more disorders particularly associated with hypopituitarism. These include spontaneous or reactive hypoglycaemia, and an increased sensitivity to insulin. Hypothermia with a rectal temperature as low as 32° C. or less may develop. Water intoxication is another important factor, due to a disturbance of water metabolism in patients with adrenal insufficiency (p. 663). Hypothyroidism is also an important component (p. 643) in the causation of coma, and failure of ventilation with anoxia and respiratory acidosis should also be considered in treating what is frequently a lethal complication of hypopituitarism.

Diagnosis. Hypopituitarism is sometimes confused with anorexia nervosa (p. 925). This psychoneurosis occurs usually in young women who for various reasons refuse to eat, and in late cases become grossly emaciated. Amenorrhoea is a constant feature. The distinguishing features lie in the history, the retention of pubic and axillary hair in anorexia nervosa, and the satisfactory response of the latter to adequate psychotherapy. In addition, anorexia nervosa is characterised by an absent appetite and gross wasting, whereas in hypopituitarism neither is striking unless some other cause is present. Assays of pituitary trophic hormones or of the products of the target glands will help to distinguish these two disorders and others which might be confused with hypopituitarism. In anorexia nervosa the endocrine failure is restricted to the gonadotrophins and ovarian hormones. The excellent response of patients with hypopituitarism to treatment with corticosteroids will also help to distinguish between the two conditions.

Treatment. The aim should be to provide adequate substitution therapy, according to the deficiencies demonstrated, so that the patient can lead a normal life. Cortisol should be given by mouth in doses of 20 mg in the morning and 10 mg in the evening. Thyroid hormone will usually be required and should be given orally as thyroxine 0·1-0·2 mg daily. It is dangerous to give thyroid hormone to these patients until they have been protected by Cortisol or a similar drug against the possibility of an Addisonian type of crisis. Excessive doses of corticosteroids may lead to hypertension. In some circumstances it may be helpful to add an oestrogen, such as Ethinyl Oestradiol 50 μg daily, and for adolescent or adult men an androgen may be required (p. 673). Fertility may be restored in young patients with appropriate gonadotrophin therapy.

Diabetes Insipidus

This rare disease is characterised by the persistent excretion of excessive quantities of urine of low specific gravity, and by constant thirst.

Aetiology. The disease develops after damage to the neurohypophyseal mechanism for the production of vasopressin. It may occur with tumours of the pituitary or after operations in this region, with a craniopharyngioma, and as a sequel to encephalitis, basal meningitis, syphilis, and fractures at the base of the skull. Metastatic disease involving the neurohypophysis may occasionally be responsible. A rare genetic form exists due to unresponsiveness of the renal tubules to vasopressin but in some cases no cause can be identified.

Symptoms. The most marked symptoms are polyuria and polydipsia. The patient may pass 5-20 or more litres of urine in 24 hours. The urine is clear and of low specific gravity (1002-1004) and osmolality. Such patients may become markedly dehydrated with a rise in plasma osmolality, if water is withheld, since they continue to secrete dilute urine in considerable volumes.

Differential Diagnosis

Diabetes Mellitus. The volume of urine increases because the excess of solute (glucose) present produces an osmotic diuresis.

Hysterical Polydipsia. This produces polyuria. In such cases if fluids are withheld for 24 hours the urine is found to concentrate to a normal specific gravity. Accurate weighing of the patient will show whether she has been drinking surreptitiously meanwhile, and should be undertaken at regular intervals during such a test in order to avoid the risks inherent in excessive dehydration. If the patient's weight falls by more than 3 per cent the test should be terminated.

Chronic Renal Disease. Glomerulonephritis, pyelonephritis, polycystic disease, partial ureteric obstruction and potassium depletion, may all be marked by an increase in the volume of urine formed in order to compensate for the loss of the capacity of the kidney to secrete a concentrated urine. Nocturia may be a more prominent complaint than polyuria.

Primary Hyperparathyroidism. This is associated with hypercalcaemia, and frequently with polyuria and polydipsia secondary to renal damage.

A positive diagnosis of diabetes insipidus depends on demonstrating that a rise of plasma osmolality induced either by withholding fluids or infusing hypertonic saline is not accompanied by a rise in the osmolality or specific gravity of the urine, but that when vasopressin is given, such a rise does occur. This final test is necessary in order to show that the kidney is capable of concentrating the urine which it cannot do in nephrogenic diabetes insipidus.

Treatment. The minimum amount of vasopressin required to keep the patient in water balance must be determined by controlling the fluid output and then reducing the dose of hormone without permitting polyuria or excessive thirst to recur.

A convenient preparation for clinical use is vasopressin tannate in oil, which may be given in doses of 0·5-1 ml (2·5-5 units) intramuscularly. The larger dose may cause headache, but if tolerated will last longer than the smaller dose. Patients usually require to repeat the injection every two to three days. It is important to warm the ampoule and to shake it vigorously before use so that the active material is resuspended before the contents are drawn up into the syringe.

Recently the use of a synthetic analogue of vasopressin (DDAVP) has been described; this can be given intranasally, and the action is sufficiently prolonged for administration once or twice daily to elicit a response as effective as vasopressin given by injection. It is not yet available commercially.

A solution of synthetic lysine vasopressin may also be administered in the form of a nasal spray absorbed through the mucous membrane of the nose. Although the effect persists for a few hours only the method is often preferable in children and is useful for others who may use it until it is convenient for them to have a further injection.

Chlorothiazide, an oral diuretic, has been used with some success to suppress the thirst and hence improve the polydipsia and polyuria of diabetes insipidus.

Chlorpropamide, up to 250 mg once daily in an adult, and clofibrate, up to 3 g daily in divided doses, may be tried separately or in combination with each other or with a thiazide diuretic, before abandoning oral treatment in favour of injections of pitressin. These oral drugs may act by stimulating the release of vasopressin where some capacity to do so remains or by sensitising the kidney to small amounts of endogenous vasopressin. The danger of intractable hypoglycaemia with chlorpropamide should not be overlooked.

Prognosis. The cause of the neurohypophyseal damage will determine the patient's progress.

THE THYROID GLAND

Anatomy and Physiology

The thyroid gland consists of an isthmus and two lateral lobes, and lies in front of and on either side of the upper part of the trachea and the laminae of the thyroid cartilage. Posteriorly it is closely related to the recurrent laryngeal nerves which lie between the trachea and the oesophagus; the gland is separated from these nerves by its fibrous sheath. The thyroid gland is provided with a rich blood supply through the superior and inferior thyroid arteries. The parathyroid glands are usually to be found lying on the posterior aspect of the thyroid in its substance or in the sheath of the gland and in relation to the upper cornu of the thymus.

Thyroxine (T_4) and triiodothyronine (T_3), the hormones secreted by the gland, are bipeptides containing respectively 4 and 3 atoms of iodine in each molecule Both are normally stored in the colloid vesicles as thyroglobulin. Because it is less strongly bound to serum proteins, T_3 acts more rapidly than T_4. It is also effective in smaller doses than T_4. Thus the effects of T_3 may be apparent in a number of hours while an equivalent dose of T_4 may take several days to be effective. Both hormones act directly on most of the tissues of the body to increase cellular metabolism.

Thyroid function is controlled by thyroid stimulating hormone (TSH) secreted by the anterior pituitary which in turn is controlled by thyrotrophin releasing hormone (TRH) secreted by the hypothalamus. TRH is a tripeptide which has been synthesised and is available for clinical use. There is also a negative feed-back mechanism whereby the thyroid hormones act principally on the anterior pituitary, but possibly also on the hypothalamus, with suppression of TSH secretion. TSH stimulates the release of thyroid hormones from the colloid into the circulation and also stimulates the synthesis of these hormones.

Calcitonin, secreted by the parafollicular C(calcitonin)-cells of the thyroid gland, is discussed on page 648.

Hyperthyroidism

The clinical condition consequent upon overproduction of T_3 or of both T_3 and T_4 is referred to as hyperthyroidism or thyrotoxicosis. In a small minority of patients the excess production of thyroid hormone is confined to T_3, but it is likely that a greater number of cases have an initial phase of excess T_3 production followed by an overproduction of both T_3 and T_4, and it is usually at the latter stage that the diagnosis is made.

Incidence. Thyrotoxicosis occurs much more frequently in women than in men (8 : 1), usually in the third to fifth decades but it may occur at any age.

Aetiology. Because of the negative feed-back referred to above, the serum TSH levels in patients with thyrotoxicosis are either low or non-existent. Cases of thyrotoxicosis due to excess TSH production or pituitary tumours are exceptionally rare. In a proportion of cases thyrotoxicosis undergoes spontaneous remission within a period of months or years, while in other cases it follows a course of intermittent and unpredictable remission and relapse. Before modern therapy became available it was commonly fatal, but spontaneous and permanent remissions also occurred.

In many patients with hyperthyroidism the IgG autoantibody, human specific thyroid stimulator (p. 36) can be detected in the serum by bio-assay and it is possible that this antibody may be the cause of hyperthyroidism in some instances. Other evidence of autoimmune activity directed against the thyroid in hyperthyroidism is the presence of lymphocytic infiltration in the gland which may be negligible, focal or extensive. Certainly thyrotoxicosis, Hashimoto's thyroiditis and primary spontaneous hypothyroidism appear to belong to a continuous spectrum of thyroid disease (p 632).

In a small percentage of patients, thyrotoxicosis is due to the presence of a hyperactive solitary nodule with suppression of the remainder of the gland through the normally functioning feed-back mechanism. In the majority of patients with hyperthyroidism the thyroid gland is either diffusely hyperactive or the gland consists of multiple active nodules interspersed with inactive areas. This latter state is probably the outcome of alternate stimulation and degeneration or results from the development of thyrotoxicosis upon a multi-nodular goitre. Toxic nodular goitres tend to occur in older patients and diffuse ones in younger subjects. Histologically the increased activity of the gland is manifest by reduction in the size of the thyroid vesicles which are relatively empty of colloid; the epithelium is tall and columnar in contrast to the flat cuboidal epithelium of the normal gland. The vasculature is markedly increased.

Clinical Features. There may or may not be clinically detectable enlargement of the thyroid gland (goitre). The increased blood supply to the thyroid may be manifest by a bruit, which should not be confused with a murmur transmitted from the aortic area into the neck or arising in the carotid artery, or in the jugular veins as a venous hum. If the increased blood supply is sufficiently pronounced there may be a thrill and the thyrotoxic gland may even be pulsatile.

Most of the clinical features of thyrotoxicosis may be explained in terms of excess production of T_3 or of T_3+T_4. The increased metabolism accounts for the loss of weight in spite of the increased appetite that is so often a striking feature in the clinical history. Occasionally, however, the patient over-compensates in terms of food intake and may gain weight. Thyroid hormones potentiate the action of the sympathetic nervous system and of adrenaline and noradrenaline.

The increased cardiac output required to meet the metabolic demands, together with the effect of T_3 and T_4 on the sympathetic nervous system, tends to produce a tachycardia or, particularly in elderly patients, arrythmias such as atrial fibrillation or ectopic beats. The patient may complain of palpitations with or without the symptoms of cardiac failure. Sinus tachycardia, persisting during sleep, is one of the earliest and most constant signs. The pulse pressure is increased and capillary pulsation may be detectable. In the presence of coincident systolic hypertension a collapsing pulse may be noted. In the older patient cardiovascular manifestations may be the only clinical evidence of hyperthyroidism and it should be remembered that thyrotoxicosis is one of the three commonest causes of atrial fibrillation.

As another consequence of the effect of excess thyroid hormones on the sympathetic nervous system, thyrotoxic patients commonly complain of increased frequency of bowel motions, usually with formed motions and there may be an element of malabsorption. A lag curve in a glucose tolerance test may be demonstrable partly as a result of intestinal hurry. A fine tremor of the fingers and retraction of the upper eyelids may occur for the same reason, while the hands are often hot and sweaty because of the increased metabolic rate and the need to lose excess heat. Intolerance of warm temperatures is characteristic. Thyrotoxic patients, although they are hyperdynamic, have a very low efficiency in terms of what they achieve. They suffer from an inability to relax both mentally and physically; anxiety is a frequent feature.

Less common clinical features that cannot be so readily explained in terms of disturbed physiology include exophthalmos (p. 641), pretibial myxoedema and finger clubbing, reduced fertility and menstrual irregularities. In addition the patient may complain of weakness of the proximal muscles in the arms and legs (thyrotoxic myopathy), which recovers when normal thyroid function is restored.

Thyrotoxic crises are now uncommon, as cases of hyperthyroidism are recognised and treated earlier and more effectively. They may be seen shortly after thyroidectomy in patients who have not been adequately prepared for operation or in patients who have been operated on for some other disability without hyperthyroidism having been recognised. Alternatively, some severe infection, for example pneumonia, may so aggravate a thyrotoxic state that a crisis is precipitated. The patient in crisis suffers from severe mental and physical exhaustion with delirium, delusions or mania, dehydration, ketosis, tachycardia, cardiac failure and inability to control body temperature, usually showing as hyperthermia.

HYPERTHYROIDISM IN THE NEWBORN AND IN CHILDREN. Thyrotoxicosis may occur rarely in the newborn when it is thought to be due to the transplacental transmission of thyroid stimulating antibody. This form of hyperthyroidism is self-limiting. If thyrotoxicosis occurs before puberty there is frequently an increase in the growth rate so that affected children are unusually tall for their age.

Differential Diagnosis. There are many conditions that may lead to loss of weight or cardiac failure and the presence of a goitre may be associated with any level of thyroid activity. The commonest problem in differential diagnosis is, however, anxiety neurosis. Provided that at least elementary radio-isotope facilities are available this differential diagnosis should not present any major problem.

Investigation. The treatment of thyrotoxicosis is so satisfactory and the opportunities for diagnosis so precise that it is not necessary to treat patients in the absence of a high degree of certainty concerning the diagnosis.

PROTEIN-BOUND IODINE (PBI). This used to be the most widely used test of thyroid function. It is however affected by many drugs including those which contain iodine so that high values are found in euthyroid patients prescribed expectorants containing iodine or tablets or capsules in which tetraiodofluorescein is the colouring agent. In addition certain radiographic studies, e.g. cholecystography, pyelography and myelography, utilise contrast media which contain iodine. An increased concentration of thyroid hormone-binding proteins, of which thyroxine-binding globulin is the most important, occurs in pregnancy and in patients on oestrogen therapy including most varieties of the contraceptive pill. This results in an elevation of the PBI without a change in concentration of free thyroid hormones which are metabolically active. The PBI is therefore of limited value in the diagnosis of thyrotoxicosis (Fig. 79).

TOTAL SERUM THYROXINE. The total serum thyroxine measured by competitive protein binding or radioimmunoassay is not influenced by exogenous iodine, but is altered in a similar manner to the PBI by factors which affect the concentration of thyroid hormone-binding proteins. It is a more useful test than the PBI.

T_3 RESIN UPTAKE. The T_3 resin uptake test is an indirect measure of circulating thyroid hormone levels. It measures the degree of saturation of the binding sites on the thyroid hormone-binding proteins. High values are found in thyrotoxicosis but low values are recorded in euthyroid patients either pregnant or on oestrogen medication. The role of such a test is in the calculation of the free thyroxine index derived from the product of either the PBI or the total serum thyroxine and the T_3 resin uptake. In euthyroid patients with abnormalities of the thyroid hormone-binding proteins and in whom the PBI or the total serum thyroxine is elevated, the T_3 resin uptake will be depressed and the free thyroxine index is more likely to lie in the normal range. As can be seen from Figure 79 the need for a T_3 resin uptake test has been largely superseded by the simplicity of the effective thyroxine ratio.

THE EFFECTIVE THYROXINE RATIO (ETR). This integrates into a single procedure the measurement of total serum thyroxine and the binding capacity of thyroid hormone-binding proteins. At the present time the ETR provides the most reliable single test of thyroid function available which can be readily carried out on a sample of serum and requires only simple radio-isotope equipment. It is not affected by contraceptive pills, pregnancy, excess iodine, or as far as is known at present, by any other drug.

THE MEASUREMENT OF THE *in vivo* UPTAKE OF RADIOACTIVE IODINE OR TECHNETIUM BY THE THYROID. The overactive thyroid synthesising excess T_4 has an increased uptake of radio-iodine which can be simply shown by measuring the proportion of an oral tracer dose of ^{131}I (half-life 8 days) or ^{132}I (half-life 2·3 hours) taken up by the thyroid in a given time (e.g. four hours) by using an appropriate 'counter' over the neck. Alternatively, an isotope of technetium (Tc99m: half-life 6 hours) may be used intravenously, giving an even smaller dose of radiation to the gland which can be regarded as insignificant. The major fallacies in such studies are caused by iodine deficiency (which can give an increased uptake measurement without the presence of thyrotoxicosis) and iodine excess (which can give a low uptake measurement in spite of the presence of thyrotoxicosis).

Either ^{131}I or Tc99m may be used to obtain a scan of the thyroid, indicating the amount and the distribution of functioning tissue. Scans are also useful in thyrotoxic patients for detecting a solitary 'hot' nodule or a retrosternal extension of the gland.

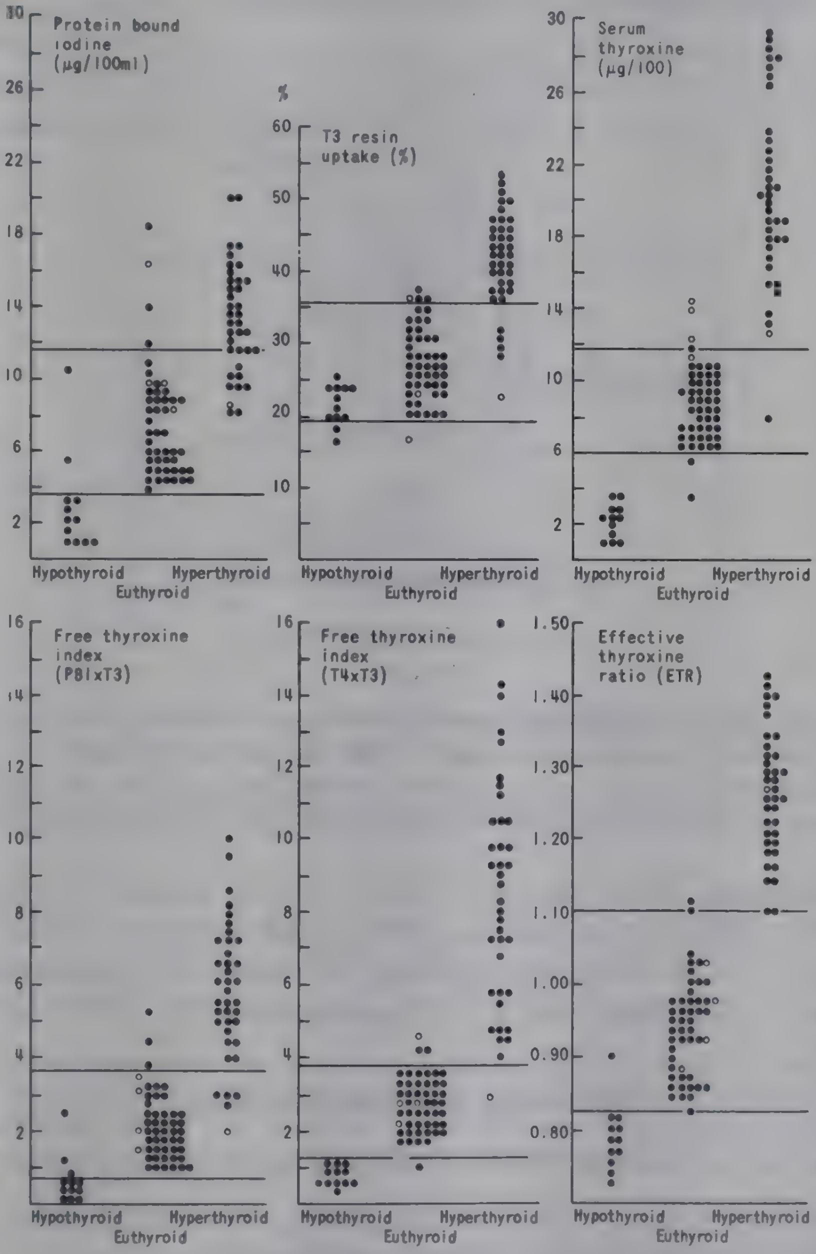


FIG. 79

Thyroid function tests in 100 consecutive patients referred to a thyroid clinic (horizontal lines indicate euthyroid range; open circles indicate patients either pregnant or on contraceptive pill). (From Toft *et al.* (1973), by permission of the Editors of *Clinical Endocrinology*.)

T_3 SUPPRESSION TEST. In patients giving equivocal results it can be determined whether or not the gland is under the control of the anterior pituitary by repeating the thyroid gland uptake measurement after the patient has taken 120 µg T_3/day in divided doses for seven days provided there is no cardiac problem. Tests involving the administration of isotopes should if possible be avoided in pregnancy although the risk with ^{132}I or Tc99m is probably negligible.

SERUM TSH LEVELS IN RESPONSE TO TRH STIMULATION. In thyrotoxicosis the secretion of TSH by the anterior pituitary is suppressed so that serum levels of TSH are either reduced or absent. Moreover, the TSH response of the pituitary at 20 and 60 minutes after the injection or ingestion of TRH is suppressed (Fig. 80). As facilities for radioimmunoassay of TSH improve this is likely to be one of the most useful tests of thyroid function.

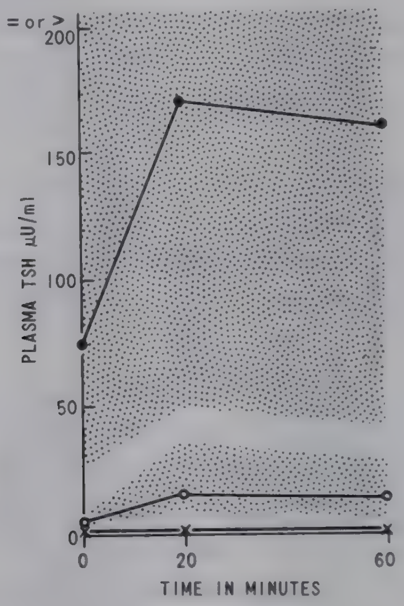


FIG. 80

The mean plasma TSH response and range (shaded area) following 200 μg TRH i.v. in 37 patients with primary hypothyroidism (●——●), 18 normal subjects (○——○) and 20 patients with thyrotoxicosis (×——×). (From Irvine *et al.* (1974), by permission of the Editors of *Companion to Medical Studies*, Volume 3. Oxford: Blackwell.)

T_3 Thyrotoxicosis. When thyrotoxicosis is due to excessive production of T_3 alone, the PBI, ETR, total serum T_4, and thyroid uptake of radio-isotopes give normal results. Until a direct measurement of serum T_3 is readily available this condition can be diagnosed only by a T_3 suppression or TRH stimulation test.

Treatment of Hyperthyroidism

Three effective methods of treating thyrotoxicosis are available:

1. Anti-thyroid drugs, such as carbimazole, supplemented as necessary by beta-adrenergic blocking agents, such as propranolol.
2. Surgery, after a euthyroid state has been achieved.
3. Radioactive iodine, with or without the use of beta-adrenergic blocking agents or anti-thyroid drugs.

ANTI-THYROID DRUGS. The site of action of the different anti-thyroid drugs is indicated in Figure 81. Most commonly used are those that act by blocking the organic binding of iodine to tyrosine, carbimazole in Europe and methimazole in North America. Other drugs which act in this way are propyl and methyl thiouracil, which may occasionally be useful in the event of hypersensitivity to the drug of first choice.

Carbimazole is given initially in full suppressive doses of 15-20 mg at eight-hourly intervals for three to four weeks according to the severity of the condition and the size of the goitre. Thereafter the dose can generally be reduced, and, as the patient's clinical state responds, the aim should be to give as little of the anti-thyroid drug as necessary to achieve a euthyroid state, which may vary between 5-30 mg per day. Overtreatment with anti-thyroid drugs will result in TSH production by the anterior pituitary with a risk of increase in size of the thyroid. In patients in whom the natural history of the underlying process is one of exacerbation and remission, stable control may only be achieved with drugs when an excess dose of carbimazole (but not greater than 45-60 mg/day) is combined with continuous thyroxine administration in a dose of 0·1-0·2 mg/day.

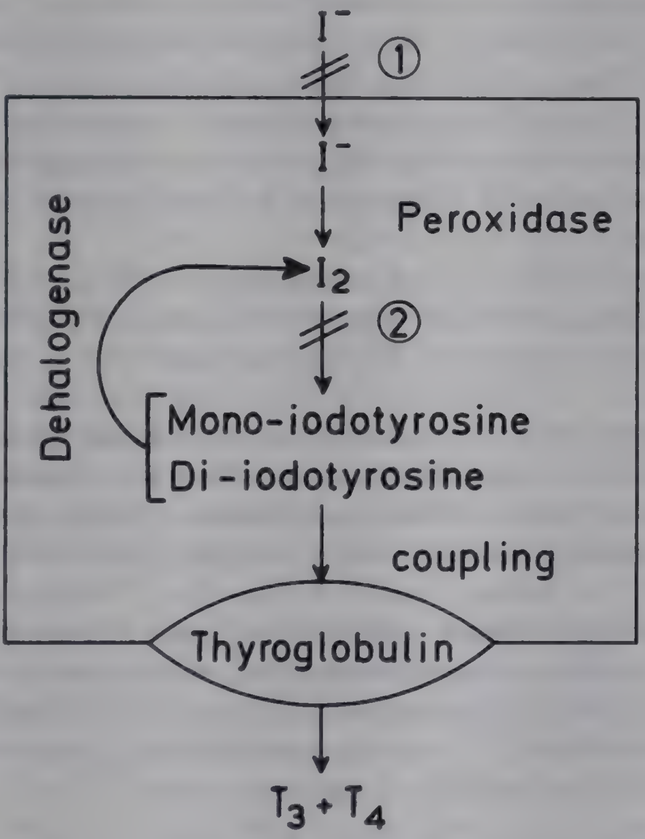


FIG. 81

Diagrammatic representation of the synthesis of thyroxine (T_4) and of triiodothyronine (T_3), illustrating (p. 646) the main sites of block induced by (1) potassium perchlorate and (2) by carbimazole, methimazole and the thiouracil group of drugs and the possible sites for enzyme deficiency in thyroid dyshormonogenesis.

Carbimazole or methimazole may be selected as the definitive therapy or, as discussed below, may be used to prepare the patient for surgery. If anti-thyroid drugs are being used as definitive therapy they should be continued for a period of at least one year and restricted to children or young adults (especially girls) who do not have marked enlargement of the thyroid. It is considered that by selecting cases in this way rather less than 50 per cent of thyrotoxic patients will go into lasting remission and will not require further therapy. Attempts to estimate the probability of achieving lasting remission by doing T_3 suppression tests while the patient continues on anti-thyroid drugs have given uncertain results.

Carbimazole, methimazole and the thiouracil group of drugs as well as potassium perchlorate, are liable to produce toxic effects, of which the commonest is skin rash and the most serious are the blood dyscrasias. Agranulocytosis is the commonest of the blood dyscrasias. Routine white cell counts are of little value in its early detection as it occurs with dramatic suddenness, usually but not necessarily in the first few weeks of treatment. Patients taking these drugs must be told to report a sore throat and to stop the drug immediately until it is clear whether agranulocytosis has occurred or not. By stopping the drug promptly and by using antibiotics prophylactically serious consequences will be avoided and the leucocyte count will return to normal within one to two weeks. Potassium perchlorate induces blood dyscrasias more commonly than other anti-thyroid drugs, including red cell aplasia which is usually lethal. For this reason, potassium perchlorate should be used only as a temporary expedient if hypersensitivity to other drugs has occurred and if radioactive iodine therapy is not an acceptable alternative. It should never be used in a dose greater than 1 g/day.

There is no place for the use of potassium iodide as an anti-thyroid drug except in the final preparation for surgery of a patient already made euthyroid with other antithyroid drugs or in the management of a thyrotoxic crisis.

BETA-ADRENERGIC BLOCKING DRUGS. These are very useful as they can produce much symptomatic improvement by countering the increased action of the sympathetic nervous system. Thus palpitations, finger tremor, anxiety, lid retraction and increased bowel activity may be alleviated with propranolol 40 mg eight-hourly or greater doses if required. Contraindications to propranolol include cardiac failure and asthma. Beta-adrenergic blocking drugs can therefore be useful during the interval of several weeks which is required for anti-thyroid drugs or radioactive iodine to be fully effective.

Sedation with diazepam (5 mg eight-hourly) may also be useful to allay anxiety until the thyrotoxicosis has been controlled.

SURGICAL TREATMENT. This is the treatment of choice if the patient is considered too young for radioactive iodine therapy (i.e. during the reproductive years) and if the anti-thyroid drug therapy has failed to produce a lasting remission or is considered unlikely to do so, or there have been sensitivity reactions to anti-thyroid drugs. Thus a thyrotoxic patient younger than 40 years with a large goitre should be treated by surgery rather than by a prolonged course of anti-thyroid drugs in the somewhat vain hope that the condition will remit in the interval and not recur when anti-thyroid drugs are withdrawn.

For a girl a thin thyroidectomy scar may be more cosmetically acceptable than a goitre. Men are thought to relapse more frequently after prolonged anti-thyroid drug therapy than are women and some authorities would advocate surgery as the treatment of choice in men under the age of 40, irrespective of the size of the goitre. The patient may or may not choose surgery once the different alternatives have been explained to him.

Before thyroidectomy is undertaken the patient must be euthyroid; the importance of this point cannot be overemphasised. While potassium iodide should not be used as a means of achieving a euthyroid state (in the absence of thyrotoxic crisis), it should be given, after a euthyroid state has been achieved, in a dose of 60 mg twice daily by mouth for 14 days before the date of subtotal thyroidectomy with or without the continued use of carbimazole or methimazole. The vasculature of the thyroid is greatly reduced making the gland appreciably firmer and operation easier for the surgeon. This effect of potassium iodide and also its effect in reducing thyroid function is transitory, making it important to reserve the use of potassium iodide for this particular situation.

Some 80 per cent of thyrotoxic patients treated by subtotal thyroidectomy should have no complications at least within a three to five year follow up. In some 15 per cent there will be either recurrence of the thyrotoxicosis or post-operative hypothyroidism requiring continuous thyroxine replacement therapy. The relative proportion of each depends on the amount of thyroid tissue left at operation. Thyrotoxic patients with high titres of thyroid complement fixing antibody in the serum before operation tend to have an appreciable degree of lymphocytic infiltration in the gland and tend to develop hypothyroidism post-operatively. While the majority of patients who become hypothyroid after surgery do so within the first six months or a year, there is a low but steady further incidence with each year after surgery making annual follow up of the patient necessary.

Damage to the recurrent laryngeal nerves occurs in a small percentage of patients and will produce temporary hoarseness with subsequent appreciable recovery as the other vocal cord compensates. Any malfunction of a vocal cord found during routine examination prior to operation would be a contra-indication to thyroid surgery, as the risk of malfunction of both cords would not be justifiable.

The parathyroid glands may be rendered temporarily ischaemic by interruption of their blood supply or they may be inadvertently removed, producing transient or permanent hypoparathyroidism respectively. The late onset of hypoparathyroidism is a complication of partial thyroidectomy which should be looked for in the follow up of surgical patients, as cataract and mental disturbance may develop insidiously in the presence of persistent mild hypocalcaemia. On account of the high incidence of recurrent laryngeal nerve damage and of hypoparathyroidism following second operations on the thyroid, thyrotoxic patients who relapse after surgery should be treated with radioactive iodine.

RADIOACTIVE IODINE. Radioactive iodine is the treatment of choice for thyrotoxic patients over the age of 40 years and also for younger patients who for some other reason appear to have a short life expectancy. It has no established complications other than the incidence of hypothyroidism in the years following therapy (Fig. 82). The incidence of thyroid cancer or leukaemia following ^{131}I therapy has been shown not to be increased. Although an effect on the spontaneous mutation of the gametes in the ovary or testis has not been proved it is difficult to disprove and therefore the administration of radioactive iodine to persons of reproductive age who have not been sterilised should be discouraged unless there is no suitable alternative.

The assessment of the appropriate therapeutic dose of ^{131}I (half-life eight days) presents some difficulties for the following reasons. The amount of functional thyroid tissue is not easy to assess with accuracy, the amount of radiation to the gland following a given dose can only be assessed by time-consuming dynamic studies, and even if a predicted amount of radiation per gram of thyroid tissue could be given, there remains the variation in radio-sensitivity among thyroid glands of different patients. For these reasons the empirical assessment of dosage using clinical criteria gives results as good as those dependent on sophisticated physical methods, provided that an avid uptake of the isotope by the gland has been established.

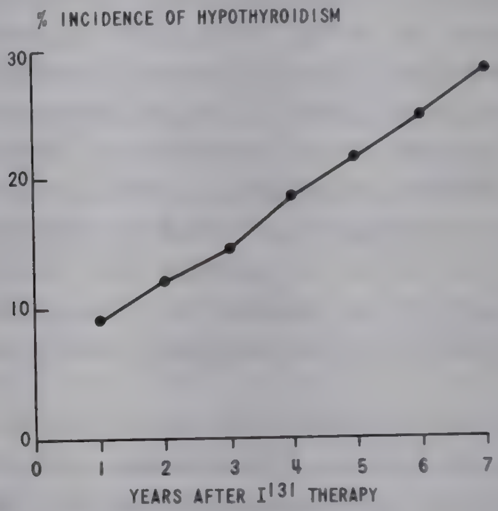


FIG. 82

The accumulative incidence of hypothyroidism after ^{131}I therapy for thyrotoxicosis.

Using a dose as small as 3 mCi ^{131}I with a diffuse uptake of the isotope as shown on a scan in a small thyroid or as high as 15-30 mCi for a large multi-nodular gland, the patient's thyrotoxicosis will be controlled in some 70 per cent of cases following a single oral administration. It may take two months or longer for the dose to be effective. If the thyrotoxicosis is severe, more rapid relief may be obtained by the addition of beta-adrenergic blocking drugs or, if cardiac failure exists, a short course of carbimazole. Carbimazole should preferably not be given prior to the administration of ^{131}I as there is some evidence that it reduces the effective radiation dose by virtue of the enzyme block which it induces. After two months a further dose of ^{131}I should be given in the 30 per cent who have not responded adequately to the first dose, using a 50 to 100 per cent higher dose in order to avoid the undesirable occurrence in a few patients of the need for repeated doses of the isotope. Some authorities administer large doses of ^{131}I to thyrotoxic patients in cardiac failure or atrial fibrillation to ensure prompt control of thyroid function with a single dose, even although this will produce a high incidence of hypothyroidism. The patient's thyroid state can then be stabilised by replacement doses of thyroxine.

The continuing incidence of new cases of hypothyroidism for many years following radioactive iodine therapy makes annual follow up essential until such time as the patient has become hypothyroid and is on a suitable life-long replacement dose of thyroxine. Some patients may maintain a euthyroid state after ^{131}I therapy for thyrotoxicosis by secreting adequate amounts of T_3 although their T_4 secretion may be subnormal.

THYROTOXIC CRISIS. The treatment of thyrotoxic crisis consists of intravenous fluid and glucose replacement; parenteral hydrocortisone on account of possible adrenocortical exhaustion; sedation and suppression of hyperpyrexia with chlorpromazine; digoxin for cardiac failure or beta-adrenergic drugs if cardiac failure is not pronounced; intravenous potassium iodide 60 mg twice daily as the most rapidly acting anti-thyroid drug; and control of body temperature by tepid sponging. Anti-thyroid drugs such as carbimazole are administered as soon as the patient is capable of taking medicaments orally. Precipitating causes, such as acute infection, must be dealt with. Thyrotoxic crisis carries a high mortality; prevention and early recognition are essential if deaths are to be avoided.

HYPERTHYROIDISM IN CHILDREN. Children, including young teenagers, have a high relapse rate following subtotal thyroidectomy, and radioactive iodine therapy is contraindicated. They should therefore be treated with carbimazole or methimazole for as many years as is necessary.

HYPERTHYROIDISM IN PREGNANCY. This may be treated with anti-thyroid drugs or by surgery provided the operation can be carried out in the middle trimester after appropriate preparation with anti-thyroid drugs and pre-operative potassium iodide. If anti-thyroid drugs are used throughout it is important to give the smallest dose that will control the thyrotoxicosis and to use an indicator of thyroid function such as the ETR that is not altered by pregnancy. Towards term, the dose of anti-thyroid drugs should be further reduced in the hope of withdrawing them for the last three weeks of pregnancy. In this way the uncommon complication of the fetus being born with a goitre may be avoided. If anti-thyroid drugs are to be continued after pregnancy the mother must not breast feed her baby. Radioactive iodine treatment should never be used for therapy in pregnancy.

Exophthalmos

The pathogenesis of exophthalmos is unknown. An exophthalmos producing substance is thought to emanate from the pituitary but its existence and nature are uncertain. Defined as the protrusion of one or both eyeballs, it may be detected clinically in the majority of cases by observing the white sclera both above and below the iris. In other cases periorbital oedema which is frequently also present may obscure this sign. The degree of protrusion and especially any progression or regression of exophthalmos should be recorded by use of an exophthalmometer.

Exposure of the cornea as a consequence of the eyelids failing to close properly will result in keratitis producing a feeling of grit in the eye and excessive watering. The conjunctiva may become injected and oedematous (chemosis).

Weakness of the extraocular muscles may give rise to an ophthalmoplegia with double vision, which is often first detected when the patient is asked to look upwards and outwards.

In a small minority of cases the exophthalmos takes a relentlessly progressive course so that the increased intra-orbital pressure causes a severe aching in the eyes and reduction in visual acuity. This constitutes an emergency situation in which relief of pressure within the orbit must be achieved if permanent deterioration in vision is to be avoided. It is best done surgically by orbital decompression, but large doses of oral corticosteroids may be used as an interim measure if surgery is not immediately possible. Fortunately, in most cases of exophthalmos the condition is less severe and after a phase of progression enters into a prolonged phase of gradual improvement although the eyes seldom return to the normal state. A lateral tarsorrhaphy, stitching together the outer margins of the eyelids, may be all that is required, thereby improving their appearance and preventing exposure keratitis. In even milder cases, chloromycetin eye drops or ointment applied at night and the wearing of slightly tinted spectacles with protective side pieces to the frames will prevent the irritation of glare, dust and wind.

In relation to the treatment of thyrotoxicosis it is particularly important that hypothyroidism is avoided as this does seem to aggravate any associated exophthalmos.

In some patients exophthalmos may precede the development of frank thyrotoxicosis and present a problem in differential diagnosis, especially if the exophthalmos is unilateral. Support for an endocrine aetiology may be obtained by demonstrating an abnormal T_3 suppression or TRH test or thyroid or gastric antibodies in the serum, or by eliciting a family history of thyroid disease.

Hypothyroidism

Hypothyroidism may be due to causes within the thyroid itself (primary) or, less commonly, to failure of TSH production following pituitary or hypothalamic disease (secondary). Hypothyroidism, especially when it is due to primary thyroid failure, is often, but not necessarily, associated with myxoedema, a thickening of the skin by deposition of a mucinous material giving the patient a characteristic appearance.

Incidence and Aetiology. Hypothyroidism most commonly occurs as a sequel of ^{131}I therapy or of surgery depending upon how frequently these forms of therapy are used for thyrotoxicosis. Primary spontaneous hypothyroidism is much less common than thyrotoxicosis and principally affects middle-aged females although it can occur in either sex at any age.

Spontaneous primary hypothyroidism may be associated with a goitre or with atrophy of the thyroid. The commonest cause of spontaneous goitrous hypothyroidism in an adult female is Hashimoto's thyroiditis. It is believed that thyrotoxicosis, Hashimoto's thyroiditis and primary atrophic hypothyroidism belong to a continuous spectrum of disease. This is characterised by: (1) a common familial trait towards organ-specific autoimmune disease in general; (2) the frequent occurrence in the serum of thyroid and gastric parietal cell antibodies, and (3) evidence of delayed cellular hypersensitivity to thyroid components as well as to such non-tissue specific antigens as mitochondria.

Less commonly hypothyroidism may be associated with other types of goitre;

for example an enzyme deficiency in the synthesis of thyroid hormones (dyshormonogenesis, Fig. 82). This form is more likely to present in children or in young adults. When hypothyroidism is secondary to pituitary insufficiency, myxoedema is unusual.

Clinical Features of Primary Hypothyroidism. *Adults*. In contrast to thyrotoxicosis the symptoms are the result of decreased metabolism, with slowing of mental and physical activity. The onset is gradual and often mistaken for ageing alone. Often the patient is the last to complain and has to be persuaded by relatives or friends to seek medical help. Frequently, the general practitioner will recognise the condition on meeting the patient for some other reason, especially after a long interval. On questioning, the patient may admit to sensitivity to cold, constipation, tiredness, vague generalised muscular pains, poor appetite, gain in weight, forgetfulness and deafness, dryness of the skin, coarse and dry hair, and disordered menstrual function. The patient may also complain of tingling in the fingers since the deposition of mucopolysaccharide may produce a carpal tunnel syndrome (p. 900), although it is to be remembered that patients with primary spontaneous hypothyroidism are also predisposed to Addisonian pernicious anaemia which may give rise to similar symptoms from polyneuropathy. Anaemia may also be a direct result of thyroxine deficiency (p. 734).

In an advanced case the face appears swollen with puffy eyelids, thick lips and an enlarged tongue. The skin is pale as a consequence of thickening with myxoedema. Sweating is conspicuously absent and the skin is dry and readily flakes on rubbing. The hair tends to be more sparse than normal and lustreless ('like a hay-stack'). Speech is slow, monotonous and husky or, in advanced instances, deep and croaky. In a milder case her friends may be repeatedly asking if she has a 'cold'.

Characteristically the pulse rate is slow, but if the condition has progressed to cardiac failure, tachycardia may be found. Commonly there is evidence of coronary artery insufficiency with angina pectoris or ECG evidence of myocardial ischaemia. On radiological examination the heart is frequently seen to be enlarged; in some cases there may be a pericardial effusion which is usually reversible with treatment. The blood pressure in uncomplicated hypothyroidism is usually normal. However, since degenerative vascular disease is common in hypothyroidism, the patient may be hypertensive. Marked slowing of the recovery phase of the ankle jerk due to delayed relaxation of the calf muscles is a very useful clinical sign. Patients with severe hypothyroidism may show frank psychosis with hallucinations and delusions ('myxoedema madness') or pass into a state of coma. In a severe case, failure to control body temperature is one of the most lethal complications; mortality rises markedly as the body temperature (measured by a low reading rectal thermometer) falls below 32° C.

While it is easy to detect the advanced case, a high index of suspicion is required to avoid missing the early case and so prevent avoidable morbidity.

Children. In children hypothyroidism presents as a deterioration in performance at school, lack of interest in games and an arrest or slowing of growth. These features will precede the development of clinically obvious myxoedema. As in adults there may or may not be a goitre.

Infants. Failure of thyroid development is responsible for the condition of cretinism. It is important to diagnose the state and initiate thyroxine replacement therapy as soon as possible. The development of the brain is dependent on the thyroid hormones so that delay in starting treatment will inevitably lead to permanent mental impairment which will be the more severe the longer the delay. The diagnostic features to look for are failure to achieve the normal milestones of development, constipation, poor feeding and a characteristic cry. Only in advanced cases will the child develop the obvious features of cretinism, which include a pot belly with umbilical hernia, coarse facial features with a broad flat nose, thick lips and a large tongue protruding from the mouth.

The defects leading to failure of thyroid development are genetic and are inherited as Mendelian recessives: in the heterozygous state the child may be goitrous only, but in the homozygous state both goitrous and a cretin.

Investigation of Hypothyroidism. SERUM PBI, ETR AND TOTAL SERUM T_4. While the PBI is more useful diagnostically in relation to hypothyroidism than it is for thyrotoxicosis, the ETR is the method of choice in terms of a single diagnostic laboratory procedure on a sample of serum.

PLASMA TSH. All patients with primary hypothyroidism have an elevated plasma TSH level but not all patients with an elevated plasma TSH necessarily have a significant degree of hypothyroidism. While a normal or low TSH level may be associated with secondary hypothyroidism due to pituitary or hypothalamic disease, a normal serum TSH level would exclude primary hypothyroidism. No purpose is achieved by doing TRH tests in primary hypothyroidism but a TRH test may be helpful in deciding whether secondary hypothyroidism is due to pituitary or hypothalamic disease.

RADIOACTIVE IODINE STUDIES. A single measurement of uptake by the gland is of very little value in the diagnosis of hypothyroidism, but the response in that uptake to adequate stimulation by parenteral TSH (10 i.u. bovine TSH on each of three consecutive days) is a good index of the capacity of the gland to function. Patients with primary hypothyroidism fail to respond. The TSH stimulation test may be used in place of radioimmunoassay of plasma TSH, but is more inconvenient for the patient.

RADIOLOGICAL STUDIES. X-ray of the epiphysis in children or of ossification centres in the wrist or heel, in infants, will indicate whether the bone age is delayed relative to the chronological age. Hypothyroidism in young people is invariably associated with impaired bone development; fragmentation of the epiphysis at the head of the femur is a striking radiological sign.

Treatment. In uncomplicated adult cases treatment with thyroxine should start with 0·05 mg/day increasing to 0·1 mg/day after three weeks provided cardiac failure or angina have not arisen. After a further 3-6 weeks the dose may be increased to 0·15-0·2 mg/day. This is now considered to be the normal full replacement dose, but a few patients may require up to 0·3 mg thyroxine/day. Patients must understand that their well-being depends on continued treatment and that they must not stop thyroxine when they feel better. There is no advantage in divided doses or taking tablets that consist of a mixture of T_3 and T_4.

In a patient known to have ischaemic heart disease it will usually be desirable to keep the dose of thyroxine between 0·05 and 0·1 mg/day and to use a beta-adrenergic blocking agent such as propanolol. In patients with secondary hypothyroidism it is essential to treat any adrenocortical insufficiency before starting thyroxine.

Myxoedema Coma with Hypothermia. Small doses of triiodothyronine (10 μg) may be given intravenously eight-hourly together with hydrocortisone and glucose and very slow restoration of the body temperature to a level of 32° C.; conservation rather than active heating should be the principle of restoration above 32° C.

Goitre

A goitre is any enlargement of the thyroid gland and on clinical examination its size, shape, consistency, symmetry, irregularity of surface, mobility or fixation relative to adjacent tissues, and the presence or absence of a bruit should be established. The level of thyroid activity should be determined in the manner already described. Goitre associated with thyrotoxicosis will not be discussed further. The common diagnosis of simple goitre is arrived at by the exclusion of other causes, such as Hashimoto's thyroiditis, subacute thyroiditis, dyshormonogenesis, or carcinoma of the thyroid.

Hashimoto's Thyroiditis

Hashimoto's thyroiditis is characteristically a firm diffuse enlargement of the thyroid gland with or without hypothyroidism. It may give rise to an aching discomfort in the neck and to mild, but never severe, obstructive symptoms. It occurs most commonly in middle-aged women. Almost all cases have antibodies in the serum to thyroglobulin or to the microsomal fraction of thyroid cytoplasm (p. 32), frequently in high titre. The ESR is often elevated. Histologically the gland consists of rather small thyroid vesicles with columnar epithelium showing eosinophilic granularity, infiltration by lymphocytes and plasma cells, sometimes with germinal centre formation and an increase in the fibrous tissue stroma. Some of these histological features may be more marked in some glands than in others or in different parts of the same gland.

In most instances there will be a satisfactory regression in the size of the goitre in response to thyroxine 0·2 mg/day, which can be hastened by giving 20 mg prednisolone eight-hourly for 10 days. Patients with Hashimoto's thyroiditis should remain on life-long thyroxine therapy irrespective of whether or not they were initially hypothyroid. In cases of diagnostic doubt a needle biopsy of the gland under local anaesthesia may be helpful. Partial thyroidectomy in such patients rapidly produces hypothyroidism if it did not already exist and is usually unnecessary.

Subacute (de Quervain's) Thyroiditis

This is a painful condition generally associated with some thyroid enlargement. It is thought to be due to a virus infection of the thyroid (e.g. Coxsackie B) and viral antibody studies are sometimes but not invariably helpful diagnostically. Thyroid function is suppressed as indicated by a very low uptake of radioactive iodine or technetium by the gland and histologically the characteristic feature is the presence of giant cells. The ESR may be markedly elevated and thyroid antibody tests are generally negative. The condition tends to regress spontaneously but may be protracted. Thyroxine 0·2-0·3 mg/day should be given to suppress TSH secretion and, in some cases, it may be necessary to give a course of oral corticosteroids or parenteral ACTH. Surgery is seldom required even in the protracted case.

Dyshormonogenesis

The patient who has a partial enzyme defect related to one of the steps in the synthesis of thyroid hormones (Fig. 81) is likely to develop a goitre in response to continued TSH secretion in the attempt to overcome the enzyme block; the increased vascularity may produce a bruit. While all these defects are rare, the commonest and the easiest to detect is a genetically determined defect in the binding of iodine to tyrosine which, when associated with nerve deafness, is known as Pendred's syndrome. Such an enzyme defect may be detected by a test with potassium perchlorate following an oral tracer dose of ^{131}I or ^{132}I, potassium perchlorate discharging out of the gland any iodine which is not organically bound.

Carcinoma of the Thyroid Gland

This is uncommon, forming about 1 per cent of all cases of cancer in Britain. It may be anaplastic or differentiated—follicular or papillary or a mixture of the two. Advanced cancers are obvious by their hardness, irregularity, adhesion to surrounding tissues and associated lymphadenopathy. Early carcinoma of the thyroid gland presents as a single nodule which almost invariably has poorer function than the surrounding normal thyroid tissue. If the nodule is sufficiently large it will be detectable as a 'cold' area on thyroid scanning. It is not possible to distinguish clinically between a single nodule that is malignant and one that is benign; all single (solitary) nodules should therefore be removed for histological examination. The proportion of solitary nodules in which malignancy is demonstrated is variously estimated at 1-10 per cent according to the histological criteria adopted.

Well differentiated thyroid tumours should be treated by total thyroidectomy followed by life-long oral thyroxine 0·2-0·3 mg/day according to the patient's age. Occasionally metastases from a well differentiated tumour may take up sufficient radioactive iodine, after all normally functioning thyroid tissue has been ablated by surgery and ^{131}I, to allow effective treatment with a further large dose of ^{131}I. Anaplastic tumours may show a good initial response to external radiotherapy, but invariably recur.

Although rare, *medullary carcinoma* of the thyroid (which arises from the parafollicular C-cells) is of particular interest as it is associated with high levels of plasma calcitonin, prostaglandins or 5-hydroxytryptamine, giving rise to symptoms such as flushing, borborygmi and diarrhoea. Patients with this form of thyroid cancer frequently have neuromas and other defects.

Benign solitary lesions in the thyroid may consist of adenomas or cysts; calcification in these cysts is common. Haemorrhage occasionally occurs into adenomas and on these grounds as well as others their removal is justified.

Simple Goitre

Simple goitre may occur sporadically, but in certain parts of the world it is found more frequently and is then referred to as endemic goitre.

Aetiology. This is not fully understood, but it is generally believed to be closely related to iodine deficiency, either because of iodine deficiency in the diet or because of factors in the diet or water such as excess calcium that may interfere with iodine absorption or because of goitrogens in the diet that prevent concentration of iodine by the thyroid. Fish is the main source of iodine and thus simple goitre due to iodine deficiency is endemic in the mountains of New Guinea, in the Alps and in the Himalayas.

Apart from the anti-thyroid drugs, a number of other drugs are known to interfere with the synthesis of thyroid hormones; thus prolonged treatment with sulphonamides or PAS may produce a goitre. Iodides taken persistently in large doses in the form of cough mixtures or 'asthma cures' may likewise cause a goitre. In each of these examples the secretion or release of thyroid hormones is suppressed and presumably the goitre results from continuing increased secretion of TSH. An intermittent shortage and supply of iodine to the gland over prolonged periods is thought to result in the multinodular character of long-standing goitres, or alternatively they may result from a patchy defect of colloid storage throughout the gland.

The incidence of endemic goitre can be greatly reduced by correcting iodine deficiency, for example, by an injection of iodised oil in the case of the New Guinea population or by legislation that ensures that table salt contains traces of iodine.

Clinical Features. A small soft diffuse simple goitre may occur at puberty or during pregnancy and may regress spontaneously thereafter, but in other cases it persists. If already present, it may enlarge further at these times. A simple goitre of long standing may achieve considerable size, become grossly nodular and give rise to obstructive symptoms, particularly if there is a retrosternal extension. Compression or deviation of the trachea may be noted clinically or radiologically and obstruction in the thoracic inlet may lead to venous engorgement of the head and neck. Bruits and thrills do not occur in simple goitres.

Treatment. The treatment of sporadic simple diffuse goitre at puberty should be with thyroxine for one to two years and not potassium iodide because of the risk of iodism. An adequate dietary intake of iodine should be ensured. Multinodular simple goitres are unlikely to respond to thyroxine and may require partial thyroidectomy for cosmetic reasons, or if obstructive symptoms are present or likely to occur. Post-operative life-long treatment with thyroxine may prevent a recurrence, although hypothyroidism after partial thyroidectomy for simple goitre is uncommon.

An adequate intake of iodine, particularly in the early years of life, is the only really satisfactory way of preventing this condition (p. 128).

Calcitonin

The parafollicular cells (C-cells) of the thyroid gland secrete a polypeptide hormone, calcitonin, apparently unrelated to the other functions of this gland. When administered by injection, the hormone lowers the serum calcium concentration. Its main effect on bone is to inhibit resorption, so that in these two important respects it could be regarded as a physiological antagonist of parathyroid hormone. It is secreted in very large quantities by medullary carcinomas of the thyroid gland, without however producing significant hypocalcaemia, and after complete removal of the source of the hormone, namely the thyroid gland. hypercalcaemia is not a feature.

Therapeutically, the hormone has been used with some success to reduce hypercalcaemia, but it is not necessarily the most effective method of doing so. For example, in hypercalcaemia associated with many forms of malignant disease, treatment with corticosteroids is to be preferred. In Paget's disease of bone it has proved valuable in providing relief from pain in the minority of cases where pain is a dominant feature. Daily injections for a period of six weeks may be followed by relief for many months, after which the course of treatment can be repeated if necessary.

THE PARATHYROID GLANDS

Anatomy. These glands, usually four in number, each measure about 5 mm in diameter. Their relation to the thyroid gland is described on page 631.

Physiology. The parathyroid glands control the concentration of calcium and inorganic phosphorus in the blood plasma, both by enhancing the removal of mineral from the skeleton, and by promoting the excretion of phosphorus by the kidney.

Calcium occurs in plasma in two forms: 'diffusible' and 'non-diffusible'. The diffusible calcium consists of ionised calcium, and a small amount of non-ionised calcium salts of organic acids. From the point of view of neuromuscular function and the occurrence of tetany, it is the 'ionised' plasma calcium concentration which is important. The non-diffusible fraction is that portion which is bound to the plasma albumin; if this is very low, the total plasma calcium might be 8 mg/100 ml or less and yet the diffusible calcium could be normal. When the plasma protein concentration is high, the plasma calcium might be

12 mg/100 ml or even more, but this would not necessarily constitute evidence of hyperparathyroidism.

Since calcitonin also affects the metabolism of calcium and phosphorus this factor should be considered in disorders of these elements. Assays of parathyroid hormone and calcitonin are still not generally available, and disorders of function have to be identified usually without this direct evidence.

Hyperparathyroidism

This term is used to describe the consequences of excessive secretion of parathyroid hormone, due either to primary disease in the parathyroid glands, or secondary usually to renal disease. *Primary hyperparathyroidism* is uncommon and is usually due to a single parathyroid adenoma. Very occasionally it may be caused by simple hyperplasia or multiple adenomas: a functioning parathyroid carcinoma can also occur.

Secondary hyperparathyroidism with hypertrophy of the glands is found in chronic renal failure. The chemical pathology involved is complex because of the primary metabolic changes of renal origin, modified in turn by the increased parathyroid activity. It also occurs as a sequel to osteomalacia associated with the malabsorption syndrome and other causes (p. 142).

The term *tertiary hyperparathyroidism* is used to describe cases of the secondary variety of long standing in which the continued stimulus is responsible for parathyroid hyperplasia being replaced by autonomous function in one or more parathyroid adenomas.

When hyperparathyroidism involves the bones to such an extent that cyst formation occurs, the condition is sometimes known as *osteitis fibrosa* or *von Recklinghausen's disease of bone.* Radiological evidence of severe involvement of the bones is seen only in a minority of cases.

Clinical Features. Some of the clinical findings in primary hyperparathyroidism are more readily understood if the action of the parathyroid hormone is recalled. In the first place the excretion of phosphorus in the urine is increased, and often that of calcium also; both phosphorus and calcium are mobilised from bone. The most significant chemical finding is an increase in the plasma concentration of calcium, occasionally to as much as 20 mg/100 ml. The plasma concentration of inorganic phosphorus may fall below 2·5 mg/100 ml. The plasma alkaline phosphatase, an index of osteoblastic activity, may be raised above the normal concentration of 3-12 (King-Armstrong) units/100 ml (22-87 i.u./*l*) depending on the degree of involvement of bone.

Renal calculi frequently form in association with the increased excretion of calcium in the urine. While many patients with hyperparathyroidism develop symptoms due to renal calculi, relatively few presenting with renal calculi owe their disorder to increased parathyroid activity. In other cases of hyperparathyroidism deposits of calcium form in and around the renal tubular epithelium (nephrocalcinosis), so that in severe cases scattered radiological opacities may be visible within the renal outline. Tubular reabsorption of water may be impaired as a consequence of deposition of calcium in the renal medulla, secondary infection, or the direct effects of parathyroid hormone. Polyuria and thirst may be sufficiently severe to suggest diabetes insipidus. In cases of long standing, and in those with associated pyelonephritis, the renal disease may progress to uraemia in spite of the relief of the hyperparathyroidism.

Patients with hypercalcaemia frequently complain of weakness, loss of appetite, drowsiness, nausea and vomiting. Some of these patients also have a peptic ulcer, and the symptoms from this source may obscure those of hyperparathyroidism. Acute pancreatitis is sometimes a presenting feature in hyperparathyroidism. In patients with bone disease, backache is a common complaint. In some, only radiological evidence of demineralisation may be found, or subperiosteal erosions may be noted in the phalanges. The 'pepperpot' appearance seen in lateral radiographs of the skull is virtually diagnostic of hyperparathyroidism. Occasionally characteristic cysts composed of fibrous tissue, osteoblasts and osteoclasts may be seen, but preoccupation with the search for bone cysts may mean that the other more widespread but less arresting changes are overlooked.

Physical examination is often unhelpful. The muscles may be hypotonic. Normochromic anaemia is common. Occasionally a parathyroid adenoma is sufficiently large and suitably placed to be palpable or even visible as a swelling in the region of the thyroid gland. Measurement of calcium excretion in the urine is a useful investigation in this disease. Provided the intake does not exceed 500 mg daily, amounts of calcium in the urine persistently in excess of 200 mg daily should be regarded as abnormal and an indication for further study.

Diagnosis. Much the most important single diagnostic feature of this condition is a raised plasma calcium concentration, and it may be necessary to carry out a series of estimations at intervals in doubtful cases, since the hypercalcaemia may be episodic. It is important that a tourniquet should not be used in obtaining blood samples, since this may be responsible for raising the plasma calcium concentration appreciably.

Radioimmunoassays of parathyroid hormone have proved valuable in localising small tumours by identifying high concentrations of hormone in specific veins in the root of the neck or mediastinum. However, a negative assay does not exclude the presence of a tumour.

A parathyroid adenoma may occasionally co-exist with secreting adenomas in the pituitary gland, the pancreas, or elsewhere; the possibility that unusual symptoms in a patient with hyperparathyroidism might be accounted for in this way should be considered.

Differential Diagnosis of Hypercalcaemia. Hyperparathyroidism must be distinguished from other conditions which may be associated with hypercalcaemia and incidentally with hypercalciuria.

1. *Immobilisation.* This factor may be of particular importance in enhancing an existing hypercalcaemia in a patient with, for example, hyperparathyroidism.
2. *Metastatic malignant disease* in bone, particularly from carcinoma of the breast.

3. *Paget's disease of bone* (p. 791), especially when the patient is confined to bed.
4. *Sarcoidosis* (p. 409).
5. *Overdosage with vitamin D* (p. 141).
6. *Myelomatosis* (p. 755).

Plasma calcium levels should be adjusted if necessary for variations in plasma albumin concentration. Taking 4·6 g/100 ml as normal, 0·09 mg/100 ml of calcium should be subtracted from the total plasma calcium value for each 0·1 g/100 ml by which the plasma albumin concentration exceeds 4·6 g/100 ml, and vice versa for readings below 4·6 g/100 ml.

Treatment. Removal of a solitary adenoma is usually sufficient to produce clinical cure, provided advanced renal disease is not already present. Patients with multiple adenomas or generalised hyperplasia of all the parathyroids may be difficult to manage, especially when the glands lie in unusual situations such as the superior mediastinum, but surgical treatment offers the only prospect of amelioration.

Hypoparathyroidism

This unusual condition may arise from a variety of causes, but with each the common clinical feature is tetany. Biochemically, a depressed concentration of calcium in plasma and a raised concentration of phosphate in plasma are characteristic.

POST-OPERATIVE HYPOPARATHYROIDISM. A transitory form of the disorder is common after a partial thyroidectomy, presumably due to interference with the blood supply of the parathyroid glands. After a complete thyroidectomy, undertaken for example for a thyroid carcinoma, permanent hypoparathyroidism may occur. Following removal of a parathyroid adenoma or carcinoma, hypoparathyroidism is likely to occur, depending partly on the extent to which biopsies of parathyroid tissue have been undertaken. The degree of post-operative hypocalcaemia is largely determined by the severity of the accompanying bone disease.

INFANTILE HYPOPARATHYROIDISM. This may be transient and associated with maternal hyperparathyroidism or calcium deficiency, or it may be associated with thymic aplasia (Di George syndrome, p. 27).

IDIOPATHIC HYPOPARATHYROIDISM. This form may develop at any age, and is sometimes associated with autoimmune Addison's disease, thyroid disease or premature ovarian failure; antibodies to parathyroid, adrenal and thyroid tissue have been demonstrated in some of these patients, so that autoimmunity is a probable cause. In these patients, in addition to tetany there may be other characteristic features including psychoses, cataracts, papilloedema, calcification in the basal ganglia, and moniliasis, particularly of the finger nails. Familial cases have been described.

PSEUDO-HYPOPARATHYROIDISM. This is the term applied to a congenital variety, which may be familial. It presents with the biochemical features of hypoparathyroidism, and in addition aberrant calcification or even ossification, cataracts, mental retardation and skeletal abnormalities, for example short metacarpals. These patients are resistant to the action of administered parathyroid hormone; their own parathyroid glands appear to be normal histologically, and high concentrations of calcitonin have been found in their circulation and in their thyroid glands.

Treatment. Commercial preparations of parathyroid hormone available for the treatment of parathyroid insufficiency are unsatisfactory because they have to be given by frequent injections, and soon become ineffective because of antibody formation. In the acute phase, calcium is given intravenously as for tetany; substitution therapy for persistent hypoparathyroidism is provided by calciferol, or an analogue of vitamin D, dihydrotachysterol (p. 654).

Tetany

Definition. An increased excitability of nerves, due to a reduction in the concentration of ionised calcium in the plasma and often accompanied by paraesthesiae and intermittent spasm of muscles, usually affecting the hands and feet.

Aetiology. Fundamentally, there are two precipitating factors, namely a low plasma calcium concentration, and alkalosis. Magnesium depletion should also be considered as a possible contributing factor, particularly in the malabsorption syndrome.

CONDITIONS ASSOCIATED WITH PLASMA CALCIUM DEPLETION

1. *Inadequate Intake or Absorption of Calcium.* Rickets (p. 137), osteomalacia (p. 142), the malabsorption syndrome (p. 942).
2. *Parathyroid Deficiency* (Hypoparathyroidism).
3. *Chronic Renal Failure* (p. 598). In this condition, although the plasma calcium concentration is often low, coincident acidosis usually prevents the appearance of tetany.

CONDITIONS ASSOCIATED WITH ALKALOSIS. In alkalosis the proportion of the plasma calcium in the ionised form may be decreased, though the total calcium concentration remains unaltered. Such a change may lead to tetany. Among the causes of alkalosis, the following should be considered.

1. Repeated vomiting of acid gastric juice, as in pyloric stenosis. Persistent vomiting with carcinoma of the stomach is unlikely to produce alkalosis as the vomitus usually contains little acid.
2. Excessive quantities of absorbable alkalis given by mouth. When this is associated with repeated vomiting it may cause severe alkalosis.
3. Hyperventilation, which is most commonly due to hysteria or some

emotional disturbance. Overbreathing lowers the alveolar carbon dioxide concentration, and consequently the plasma CO_2 tension.

4. Some cases of primary aldosteronism (p. 659).

Clinical Manifestations of Tetany

In *children* a characteristic triad of carpopedal spasm, laryngismus stridulus and convulsions may occur, though one or more of these may be found independently of the others. The hands in carpal spasm adopt a characteristic position. The metacarpophalangeal joints are flexed and the interphalangeal joints of the fingers and thumb are extended (*main d'accoucheur*). Pedal spasm is much less frequent. Laryngismus stridulus is caused by spasm of the glottis.

In *adults* convulsions and laryngismus stridulus are rarely encountered. Carpopedal spasm is the usual finding, the patient complaining of painful cramps in the limbs and tingling in the hands and feet.

Latent tetany may be present when signs of overt tetany (e.g. spontaneous carpopedal spasm) are lacking. It is recognised by eliciting the following signs:

1. *Trousseau's Sign.* Inflation of the sphygmomanometer cuff on the upper arm to more than the systolic blood pressure is followed by characteristic spasm in the forearm muscles within four minutes.

2. *Chvostek's Sign.* A tap over the facial nerve in the parotid gland stimulates the hyperexcitable nerve, and the facial muscles contract. A response may frequently be elicited in normal persons.

Treatment

CONTROL OF TETANY. Injection of 20 ml of a 10 per cent solution of calcium gluconate slowly into a vein will raise the plasma calcium concentration immediately. An intramuscular injection of 10 ml may also be given to obtain a more prolonged effect.

In alkalotic tetany the plasma calcium concentration is normal, but the ionised calcium is reduced. In severe cases intravenous calcium gluconate often relieves the spasm, while more radical treatment of the alkalosis, which will vary with the cause, is being applied:

1. In persistent vomiting, intravenous saline is the most effective treatment.

2. When alkalis have been given to excess their withdrawal may suffice to stop the tetany, but if not, ammonium chloride 2 g should be given four-hourly until relief has been obtained.

3. The inhalation of 5 per cent carbon dioxide in oxygen may be prescribed for the correction of the alkalosis of hyperventilation, or more simply, the patient should be made to rebreathe her own expired air from a suitable bag. If the patient is then asked to overbreathe until tingling is again felt in the fingers (usually within five minutes), she is so impressed by the demonstration of the origin of her symptoms that this sequence of events does not recur. The hysterical patient should also be treated by appropriate psychotherapy (p. 925).

If tetany is not relieved by giving calcium the administration of magnesium may be required.

TREATMENT OF THE UNDERLYING CONDITION

1. Rickets (p. 139) and osteomalacia (p. 143).
2. The malabsorption syndrome (p. 495).
3. Chronic renal failure (p. 600). In this condition temporary benefit is usually the most that can be expected unless haemodialysis or transplantation is being employed; symptoms should be treated as they arise with parenteral calcium.
4. When tetany follows removal of a parathyroid gland and if there is any residual parathyroid tissue, this usually undergoes compensatory hypertrophy. In the interval intravenous calcium gluconate may be required to control the tetany. If all the parathyroid tissue has been removed, prolonged replacement therapy with calciferol is commonly used to maintain a normal plasma calcium concentration. One tablet (1·25 mg) daily is usually adequate, but less, or more, may be required. The maintenance dose is determined by careful monitoring of the plasma calcium at intervals, as persistent hypercalcaemia which might follow prolonged high doses of vitamin D would lead to widespread metastatic calcification and rapidly progressive renal failure (p. 597).

Dihydrotachysterol, an analogue of vitamin D, is also a useful substitute in parathyroid insufficiency, but it is more expensive than calciferol.

THE ADRENAL GLANDS

Anatomy and Physiology

The adrenal glands lie in relation to the upper poles of the kidneys. Each consists of an inner medulla which secretes adrenaline and noradrenaline and an outer cortex formed of three layers. These, from without inwards, are the zona glomerulosa, fasciculata and reticularis. Although over 40 steroid compounds have been extracted from the adrenal cortex, the principal hormones secreted are cortisol, corticosterone, aldosterone, androstenedione, androsterone and dehydroepiandrosterone. These hormones are grouped according to their main metabolic activity, i.e. glucocorticoids, mineralocorticoids or androgens.

Adrenocorticotrophic hormone (ACTH) is the only substance so far recognised that will alter the rate of biosynthesis and secretion of the glucocorticoid cortisol from the zona fasciculata and reticularis. ACTH also increases the secretion of the adrenal androgens such as androstenedione. Aldosterone (mineralocorticoid) secretion by the zona glomerulosa is primarily controlled by the renin-angiotensin mechanism (p. 582) and is not markedly affected by physiological alterations in ACTH levels.

Three major mechanisms appear to control ACTH release and thus cortisol secretion, namely:

1. negative feedback;

2. diurnal (nyctohemeral) rhythm;
3. stress.

The negative feedback mechanism is thought to operate via the hypothalamus rather than directly on the pituitary but there is still uncertainty about this. The corticotrophin releasing factor (CRF) from the hypothalamus has not yet been isolated in man and cannot be measured in serum. Reduction in the level of plasma cortisol leads to an increased secretion of ACTH from the basophil cells of the anterior pituitary, probably effected by increased release of CRF from the hypothalamus. Conversely, a rise in plasma cortisol produces a rapid suppression of the secretion of ACTH. Cortisol secretion is thus presumably determined at the hypothalamic level, controlled by an inherent diurnal rhythmicity of CRF secretion and consequently of ACTH release. The normal levels of plasma cortisol in an unstressed subject would be 6-22 μg/100 ml at 0800 to 1000 hours and less than 7 μg/100 ml at 2200 to 2400 hours.

Stress can override the negative feedback mechanism and the diurnal rhythm. Trauma, pain, apprehension, nausea, fever and hypoglycaemia have all been shown to be effective forms of stress in this regard.

It is from an understanding of the normal physiological mechanisms involved in adrenocortical hormone secretion that procedures have been developed to test various components of the hypothalamo-pituitary-adrenal axis and so determine the site of the lesion in cases of adrenocortical over- or underactivity.

The glucocorticoids have effects which are antagonistic to insulin, tending to raise the blood sugar by converting amino acids derived from protein breakdown into glucose (gluconeogenesis). Glucocorticoids such as cortisol have other important actions including the suppression of inflammatory reactions which may occur in response to injury, infection or immunological mechanisms. Glucocorticoids are also lipogenic and have some mineralocorticoid effects especially when used in pharmacological doses.

Aldosterone is the naturally occurring mineralocorticoid. It produces retention of sodium and increased excretion of potassium and if given in pharmacological doses over a prolonged period also causes hypertension. Weight for weight aldosterone has far greater mineralocorticoid activity than the glucocorticoids.

In addition to androgens, the adrenal cortex also synthesises oestrogen and progesterone in small quantities in both sexes. The nitrogen-retaining (anabolic) activity of the androgenic hormones is antagonistic to the catabolic effect of the glucocorticoids.

Hyperfunction of the Adrenal Gland

Cushing's syndrome can be defined as the symptoms and signs associated with prolonged exposure to inappropriately elevated plasma corticosteroid levels. The syndrome may be divided into two main groups depending on whether or not the condition derives from exposure to excessive ACTH.

ACTH dependent causes:

1. Iatrogenic—administration of excessive quantities of ACTH or its synthetic analogues (p. 670).

2. Pituitary-dependent bilateral adrenocortical hyperplasia, conventionally called Cushing's disease.
3. The ectopic ACTH syndrome—secretion of ACTH by malignant or benign tumours of non-endocrine origin.

Non-ACTH dependent causes:

1. Iatrogenic—administration of supraphysiological doses of corticosteroids (p. 670).
2. Adenomas or carcinomas of the adrenal cortex.

Cushing's syndrome associated with pituitary-dependent adrenocortical hyperplasia and adrenal tumours is four times more common in women than in men. This contrasts with the male predominance found in Cushing's syndrome secondary to the ectopic production of ACTH by non-endocrine tumours, commonly carcinoma of the bronchus. In the non-ectopic group the peak age incidence is between 35 and 50 years whereas it is later in the others.

Clinical Features of Cushing's Disease. These can be interpreted largely in terms of the action of the glucocorticoids described above. Thus the gluconeogenic effect is seen as an elevation of the blood glucose level and glycosuria if the renal threshold is exceeded. A proportion of patients develop diabetes with characteristically abnormal glucose tolerance curves. The effect on the blood sugar is however not invariable because of other mechanisms that counteract any disturbance in carbohydrate metabolism, such as insulin secretion. The breakdown of protein to form glucose is reflected in the reduction of muscle, skeletal and connective tissue, leading to weakness, proximal myopathy, osteoporosis, easy bruising and purple striae of the skin over the abdomen, buttocks and thighs. Osteoporosis may be sufficiently severe to produce backache with or without radiological changes in the vertebral bodies progressing to a kyphosis and collapse with shortening of the vertebral column.

The most striking features of Cushing's disease are the moon face, central obesity, buffalo hump (accumulation of fat at the lower part of the back of the neck), plethora and hypertension that are associated with the redistribution of body fat and sodium and fluid retention produced by the weak but unopposed mineralocorticoid action of glucocorticoids. The loss of potassium may also contribute to muscular weakness. The overproduction of adrenal androgens may lead to the development of hirsutism and acne in some patients with perhaps temporal recession of scalp hair in females. Amenorrhoea or other disorders of menstrual function are common. Mental symptoms, in particular depression, may be prominent.

The pituitary gland in Cushing's disease is seldom grossly enlarged either in the presence of hyperplasia or of an adenoma of the basophil or chromophobe cells. Although some enlargement may be detectable on X-ray of the pituitary fossa, often no radiological abnormality can be seen. Expansion of the pituitary fossa and pressure on the optic chiasma may occur due to an adenoma following treatment by bilateral adrenalectomy and replacement doses of steroids, with the development of bilateral temporal visual defects. In such cases the very high levels of ACTH in the serum (Fig. 83) together with the secretion of melanocyte stimulating hormone (MSH) cause marked brown pigmentation of the skin (Nelson's syndrome).

In the case of an adrenocortical tumour affecting the zona fasciculata/reticularis, the clinical features will depend on the type of steroid that the tumour is synthesising. If the tumour is making glucocorticoids almost exclusively the clinical features will be indistinguishable from Cushing's disease, whereas if the tumour is making predominantly androgens the female patient will be virilised, with pronounced hirsutism, deepening of the voice, recession of the hair on the forehead, acne and clitoral enlargement, possibly with increased libido. In males an adrenal tumour may induce feminisation if the tumour is making oestrogens predominantly. Although many adrenocortical adenomas are benign, functional carcinomas do occur with metastases to other organs.

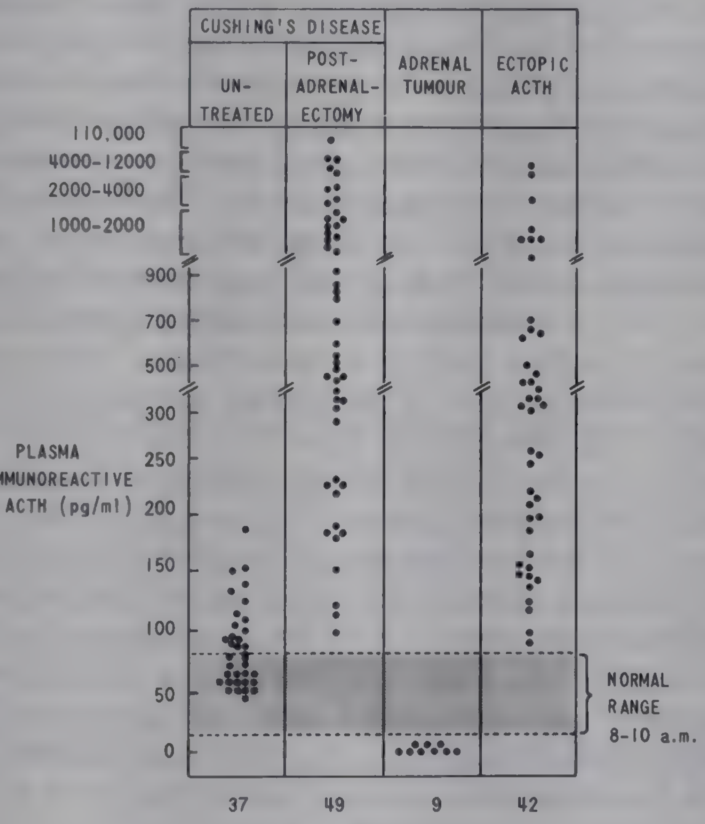


FIG. 83

Plasma immunoreactive ACTH levels in 137 cases of Cushing's syndrome. (From Besser and Edwards (1972), *Clinics in Endocrinology*, vol. 1, No. 2, p. 451.)

When Cushing's syndrome is due to the production of ectopic ACTH the striking features are the rapid development of brown pigmentation due to the very high plasma levels of ACTH or MSH or biologically active analogues. Frequently such patients show a marked alkalosis and potassium depletion. Characteristically they do not appear Cushingoid (moon face and central obesity) presumably because the underlying malignant process and the short survival time prevent this. The prognosis for such patients is generally measured in weeks or months.

Differential Diagnosis. The main differential diagnosis of Cushing's disease or syndrome is simple obesity and simple hirsutism, especially when either is associated with mild hypertension and menstrual irregularity or when both co-exist. Functional ovarian tumours may give a similar clinical picture. It can sometimes be difficult to decide when to investigate and when to exclude the possibility of Cushing's disease or syndrome on clinical grounds alone. Overactivity of the adrenal cortex is comparatively rare while simple obesity, hirsutism, menstrual irregularities and hypertension are common.

Investigation of Suspected Overactivity of the Zona Fasciculata/Reticularis. Disordered function of the zona fasciculata/recticularis is almost invariably reflected in an alteration of the normal diurnal rhythm of cortisol secretion with high levels of plasma cortisol in the evening; the simple measurement of plasma fluorigenic corticosteroids by Mattingly's method can be taken as a close approximation to the level of plasma cortisol. The demonstration of such an abnormality does not establish the diagnosis since stress, obesity or hypertension may produce similar findings. In subjects with normal adrenocortical function the secretion of cortisol should be readily suppressible with biologically active analogues of cortisol such as dexamethasone. These substances do not contribute to the measurement of fluorigenic corticosteroids which therefore continue to reflect the endogenous level of cortisol in the plasma. Normal subjects and patients suffering from simple obesity or from hypertension due to causes other than Cushing's syndrome will show suppression of cortisol secretion following 0·5 mg oral dexamethasone six-hourly for 48 hours. The majority of patients with Cushing's disease will show significant suppression following 2·0 mg dexamethasone six-hourly for 48 hours, while most patients with adrenal tumours and the ectopic ACTH syndrome will fail to do so at this dosage. The most sensitive test of glucocorticoid production is the cortisol secretion rate (normal range 9-31 mg/24 hours); this involves the administration of ^{14}C-labelled cortisol and the measurement of one of its metabolites in a 24-hour collection of urine.

An assessment of adrenal androgen secretion may be made by measuring the 17-oxosteroid excretion in 24-hour urine samples and in the rare feminising adrenal tumour in males the oestrogen output may also be estimated in urine.

Once a diagnosis of excess activity of the zona fasciculata/reticularis has been made, some indication of the cause may be obtained by radioimmunoassay of the plasma ACTH concentration. As shown in Figure 83, moderately elevated levels are seen in Cushing's disease, low or undetectable levels occur in adrenal adenoma and strikingly high levels occur in the ectopic ACTH syndrome. Further information may be obtained by adrenal arteriography. In the ectopic ACTH syndrome the tumour producing the ACTH is frequently highly malignant and is usually only too obvious.

About 70 per cent of cases with overactivity of the zona fasciculata/reticularis are due to Cushing's disease, (i.e. pituitary dependent bilateral adrenal hyperplasia), 20 per cent to an adrenal adenoma or carcinoma and 10 per cent to the ectopic ACTH syndrome.

Treatment of Overactivity of the Zona Fasciculata/Recticularis. This clearly depends on the establishment of the cause. The adrenal which is the site of an adenoma or carcinoma should be removed surgically. In the case of the ectopic ACTH syndrome the primary tumour should be removed but unfortunately this is rarely possible. Transitory improvement may be achieved by using metyrapone (p. 665) or amino-glutethamide to block cortisol synthesis together with appropriate electrolyte replacement with particular reference to potassium.

In relation to the more common Cushing's disease opinions vary as to the best treatment. The most usual is bilateral adrenalectomy followed by replacement steroid therapy (p. 666). Nelson's syndrome (p. 657) may be a late postoperative complication; this can be prevented either by giving external irradiation to the pituitary at the time of bilateral adrenalectomy or should there be evidence of rising plasma ACTH levels in excess of 1,000 pg/ml after the operation. Those authorities who endeavour to treat the condition more rationally by implantation of radioactive yttrium into the pituitary achieve somewhat variable results which are sometimes highly successful with control of ACTH secretion and preservation of other pituitary functions. Proton beam irradiation to the pituitary may be the treatment of choice in the future.

Overactivity of the Zona Glomerulosa (Aldosteronism)

This necessarily means hypersecretion of aldosterone and it may be primary in origin or secondary to some other pathology.

In *primary aldosteronism*, usually associated with an adenoma and known as Conn's syndrome, the most consistent symptom is weakness, often episodic, and attributable to potassium deficiency. Polyuria and polydipsia, also due to the effects of potassium depletion and impaired renal tubular reabsorption of water, commonly occur. Tetany may be an occasional presenting symptom precipitated by the metabolic alkalosis associated with potassium depletion. The blood pressure is usually raised and the condition may be mistaken for essential hypertension or for myasthenia because of the weakness. Oedema is most unusual. Primary aldosteronism should be treated by removal of the affected adrenal.

Secondary aldosteronism occurs in cirrhosis of the liver with ascites, in the nephrotic syndrome and less consistently in severe cardiac failure. Potassium depletion may not be detected in the plasma, hypertension is less likely to occur and oedema is usual. The use of spironolactone in the management of these conditions is discussed on pages 250 and 564. The secondary form may also occur in patients with unilateral renal ischaemia due to renal artery stenosis, a form which can occasionally be cured by surgical correction of the arterial defect.

Insufficiency of the Adrenal Cortex

Inadequate secretion of the adrenocortical hormones may be primary from acquired disease of the adrenals (Addison's disease) or because of congenital enzyme deficiency in relation to the synthesis of adrenocortical hormones (congenital adrenal hyperplasia). It may be secondary to failure of ACTH secretion due to pituitary or hypothalamic disorders (Fig. 84).

Addison's Disease

Autoimmune adrenal failure (78 per cent) and tuberculous destruction of the adrenal (21 per cent) are the commonest causes of Addison's disease in the developed countries, while other causes such as those listed in Figure 84 are rare. When acute adrenal failure occurs during the course of an infection with septicaemia (usually meningococcal) it has the eponym Waterhouse-Friderichsen syndrome. Autoimmune adrenal failure (previously referred to as 'idiopathic' or 'simple' atrophy) affects females twice as frequently as males and may occur at any age. Tuberculous Addison's disease has an equal sex incidence. Autoimmune adrenal failure is characterised by adrenocortical antibodies in the serum and cell mediated hypersensitivity to adrenocortical antigens and a high incidence of other organ-specific autoimmune diseases such as thyrotoxicosis, Hashimoto's thyroiditis, primary atrophic hypothyroidism, pernicious anaemia, premature ovarian failure, idiopathic hypoparathyroidism and also insulin dependent diabetes. Histologically both adrenals show atrophy of the cortical

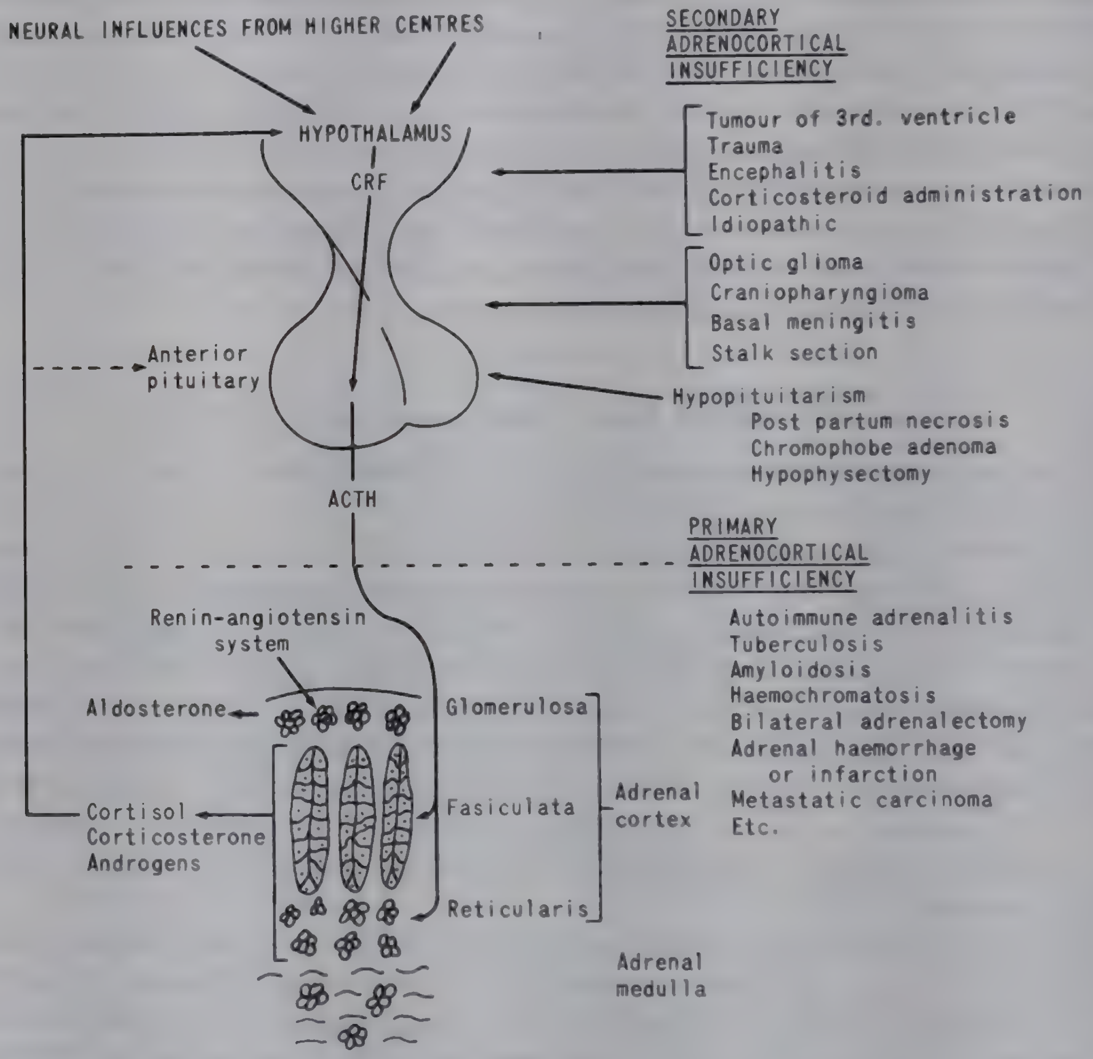


FIG. 84

Diagrammatic representation of the control of adrenocortical function and the sites of action of the various causes of disordered function.

cells in all three zones with lymphocytic infiltration and increase in fibrous tissue. The medulla is not significantly affected. The adrenals are usually smaller than normal and appear atrophic.

In tuberculous destruction of the adrenals there is caseation with giant cells and calcification which may be detected radiologically in long-standing cases.

Clinical Features. The onset of adrenal insufficiency may be acute or chronic, or more commonly acute following upon chronic. The main clinical features of chronic primary adrenal insufficiency are weakness, weight loss, hyperpigmentation or vitiligo, hypotension and gastrointestinal disorders. The invariable symptoms of tiredness and malaise, both physical and mental, gradually increase. Loss of weight does not occur until the adrenal failure is well advanced and then it is invariable. Anorexia, nausea and constipation alternating with diarrhoea occur with increased frequency as the disease progresses. Eventually in adrenal crisis the gastrointestinal complaints may be the outstanding feature and an erroneous diagnosis of severe gastroenteritis may be made; pain may simulate an acute abdomen. A wrong diagnosis may cost the patient his life.

Pigmentation of the skin is often the clinical sign that first raises the suspicion of primary hypoadrenalism. A history of its recent onset is more significant than pigmentation of long standing. This feature is due to increased melanin and is most obvious in regions normally pigmented and exposed to light or pressure, e.g. face, neck, back of hands, knuckles, elbows and knees, or in areas of the body subject to friction and in skin creases, particularly in the palms. The mucous membranes of the mouth, the conjunctivae and the vagina may also become pigmented. Scars that have been present before the onset of primary adrenal failure remain unpigmented in contrast to those that are acquired after the onset of adrenal failure. Pigmentation may precede the other features of hypoadrenalism by many years. It often manifests itself initially by the patient acquiring a much better suntan than usual and the tan taking longer to disappear. The progressive pigmentation is believed to be due to increased secretion of MSH by the pituitary which occurs simultaneously with augmented ACTH release and possibly in part to ACTH itself. Vitiligo, patchy areas of depigmentation of the skin surrounded by increased pigmentation, occurs in 10 to 20 per cent of patients with Addison's disease, particularly in dark skinned races.

The patient may give a history of very slow recovery from an illness or operation, having escaped an acute crisis at such a time. Likewise, there may be a history of extreme sensitivity to drugs such as morphine or pethidine.

Hypotension is almost invariable whether the patient is erect or supine. It is uncommon for a patient with primary adrenocortical failure to have a systolic blood pressure greater than 110 mm Hg before appropriate replacement therapy is started. Normal reflex maintenance of the blood pressure is impaired and dizziness and syncopal attacks may result from postural hypotension.

Reactive hypoglycaemia after a carbohydrate meal may occur, cortisol being one of the physiological antagonists of insulin. Hypoglycaemia is usually manifest by tiredness and lethargy, the patient having more than usual difficulty in getting up in the morning.

Loss of body hair, especially in the female, is occasionally found but is generally not so marked as in hypopituitarism. Menstrual disorders, usually amenorrhoea, are common during the onset of the disease before treatment is instituted. A significant proportion of patients with autoimmune Addison's disease suffer from premature failure of ovarian function on account of an immunological reaction against antigens that are shared between the adrenal cortex and the steroid producing cells of the ovary.

Secondary Adrenal Insufficiency

The secretion of ACTH and TSH is more resistant to pituitary damage than is the secretion of the gonadotrophins or growth hormone, so that patients with adrenal insufficiency secondary to organic pituitary disease generally show clinical features of impaired gonadotrophin secretion or of growth hormone secretion if the patient is of appropriate age for such features to be manifest. Thus a patient with secondary adrenal insufficiency will differ from one with Addison's disease by showing pallor instead of increased pigmentation of the skin. The skin is usually fine provided hypothyroidism is not pronounced, and there is marked loss of axillary and pubic hair. Because the secretion of aldosterone is largely independent of the pituitary, the blood pressure is better maintained than in primary adrenal insufficiency and the threat to life is less marked. Otherwise the symptoms are similar to those of primary adrenal insufficiency. In the absence of ACTH secretion the zona fasciculata/reticularis undergoes disuse atrophy.

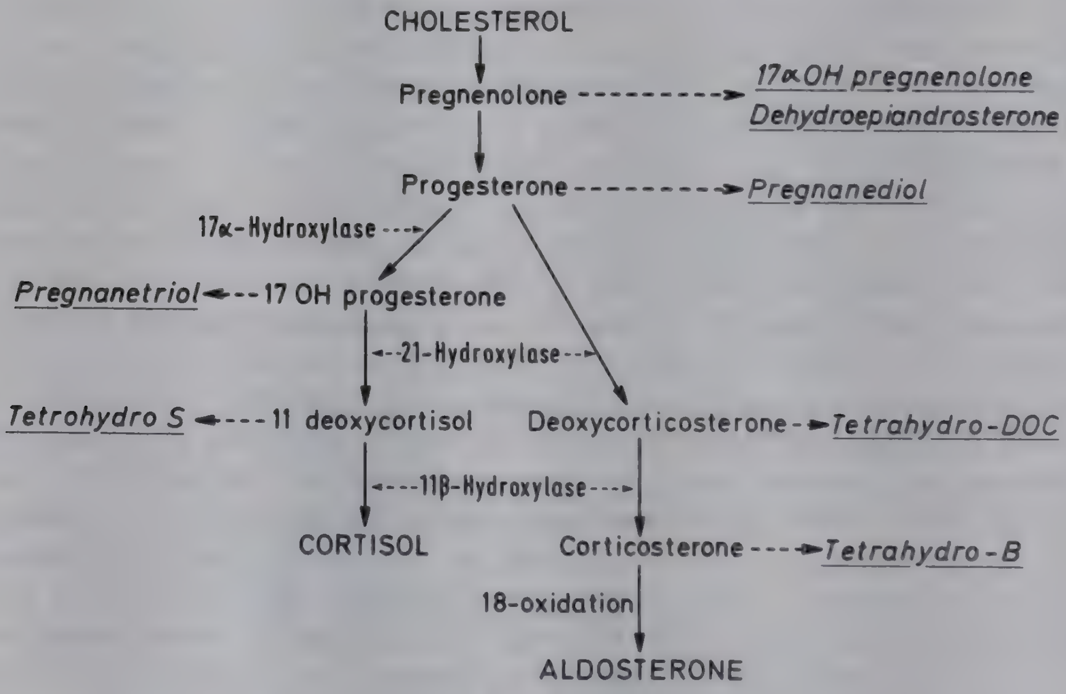


FIG. 85

The enzymatic steps involved in the synthesis of cortisol and aldosterone in the adrenal cortex and the urinary metabolites (indicated in italics) that are likely to be increased should there be an enzyme block (e.g. in congenital adrenal hyperplasia) at the next enzymatic step. The fall in the secretion of cortisol will activate the anterior pituitary to secrete ACTH with increased stimulation of the enzymatic steps preceding the block.

Adrenal insufficiency induced by the prolonged use of therapeutic doses of corticosteroids is discussed on page 670.

Congenital Adrenal Insufficiency with Hyperplasia

The synthesis of aldosterone and of the glucocorticoids involves a series of enzymatic steps involving hydroxylases. Congenital adrenal insufficiency may present at birth, in infancy, or in childhood, depending on the precise type and severity of the hydroxylase deficiency. In the attempt to overcome the enzyme block, negative feedback control results in increased secretion of ACTH with overproduction of the compounds synthesised before the enzyme block is encountered. This usually means the production of large quantities of androgenic steroids. The metabolic consequences of deficiency of enzymes at the different stages of synthesis of cortisol and aldosterone are illustrated in Figure 85. Thus at birth, female infants may show signs of virilisation with clitoral hypertrophy and variable degrees of fusion of the labia. Male infants particularly may die in adrenocortical insufficiency, because the genital stigmata to be seen in female infants are not present to provide an appropriate warning of adrenal disease. If the enzyme defect is less severe the patient may survive infancy and present in childhood with evidence of precocious puberty. Growth may be abnormally advanced at first but is restricted later by early fusion of the epiphyses. Thus patients with mild examples of the enzyme defects usually come under supervision when excessive tallness, premature appearance of secondary sexual characteristics or libidinous tendencies arouse parental anxieties.

Investigation of Adrenal Insufficiency

The symptoms and signs of adrenal insufficiency are so non-specific that confirmation of the diagnosis must be sought whenever suspicion arises. Tests of adrenocortical function are based on:

1. The metabolic effects of corticosteroids.
2. The measurement of cortisol levels in the resting state and following stimulation.
3. Measurement of ACTH levels in the plasma.

1. **Metabolic Effects.** Patients with Addison's disease, in contrast to those with secondary adrenal insufficiency, may show alteration in their serum electrolytes with depressed sodium and elevated potassium levels; this is by no means invariable even in advanced cases and must not be depended upon for diagnosis. Some degree of hypoglycaemia may occur but this also is of little diagnostic value. In past years the inability of patients with adrenal insufficiency to excrete a water load rapidly was used as a diagnostic test.

2. **Cortisol Levels.** Provided the patient is not in crisis or approaching crisis, time may be taken to determine the presence or absence of a diurnal rhythm in plasma cortisol levels by taking blood at 0900 hours and 2300 hours for two or three consecutive days for determination of fluorigenic corticosteroid levels

before treatment is started. Low levels and the absence of a diurnal rhythm could be due to a lesion at any point in the hypothalamic-pituitary-adrenal axis. Normal levels and a normal rhythm would suggest that the whole axis is normal, but the possibility exists that, while overall function is maintained there has been a significant reduction in reserve function which could be of paramount importance in times of stress. For this reason, if either primary or secondary adrenal insufficiency is suspected clinically, the diurnal rhythm studies should be supplemented by stimulation tests.

The stimulation tests should be done in a logical sequence, starting with the administration of ACTH or a potent analogue. This should be done whether the clinical suspicion is of primary or secondary adrenocortical insufficiency. The preparation of choice is tetracosactrin depot, which consists of the biologically active first 24 amino acids of human ACTH adsorbed to zinc phosphate to give a preparation with a duration of action of at least 24 hours when given in an intramuscular dose of 1·0 mg. The plasma fluorigenic corticosteroid level may be measured at 30 minutes, 60 minutes and five hours after the injection. For a normal result the initial basal level should be greater than 5 μg/100 ml, the increment after 30 minutes should be more than 7 μg/100 ml and the level eventually exceed 18 μg/100 ml. If all three of these criteria are met it is unnecessary to proceed further but if this initial response is impaired the plasma levels should be taken at five hours after the injection and the procedure repeated on the following two days.

In secondary adrenal insufficiency there is a characteristic stepwise increase in plasma cortisol levels on each day of tetracosactrin depot administration, while in primary adrenal insufficiency (Addison's disease) there is little or no response. For practical purposes the criteria for primary adrenal insufficiency would be failure of the plasma fluorigenic corticosteroid levels to rise above 25 μg/100 ml by 5-12 hours after the third intra-muscular injection of 1·0 mg tetracosactrin depot given on three consecutive mornings.

Since highly biologically active analogues of cortisol, such as betamethasone or prednisolone, do not cause fluorescence in the Mattingly procedure, ACTH stimulation tests can be effectively carried out even though the patient may have recently started replacement therapy using these analogues.

Insulin induced Hypoglycaemia. In a patient in whom secondary adrenocortical insufficiency is suspected, the next procedure should be insulin induced hypoglycaemia. Unless radio-immunoassay of ACTH levels is readily available, insulin induced hypoglycaemia should be undertaken only after it has been shown that the patient's adrenal cortex is fully responsive to ACTH stimulation, because the patient's own adrenals will be used to assay the ACTH secreted from the pituitary in response to the hypoglycaemia. Insulin induced hypoglycaemia is a safe procedure provided certain precautions are taken. A history of epilepsy is a contraindication. Patients with hypopituitarism are very sensitive to small doses of insulin and the dose should not exceed 0·1 unit soluble insulin/kg body weight. This is given in the form of a single intravenous injection, an in-dwelling cannula with a slow infusion of saline having previously been established. The patient must be observed throughout the test with the physician at hand checking the condition of the patient repeatedly. A good index of adequate hypoglycaemia is the presence of sweating. Should hypoglycaemia become profound and the clinical features indicate that the test should be abandoned, the situation can be readily corrected by giving glucose via the intravenous cannula and hydrocortisone if necessary. In addition to the clinical criteria of sweating, the blood sugar should fall to less than 40 mg/100 ml or to less than 50 per cent of the basal level at 30 minutes, whichever is the lower. Blood glucose and plasma fluorigenic corticosteroid levels should be estimated half hourly for 90 mins. Normal peak values of the latter show a mean of 28 μg/100 ml with a range of 20-38 μg/100 ml, the increment being a mean of 15 with a range of 7-24 μg/100 ml.

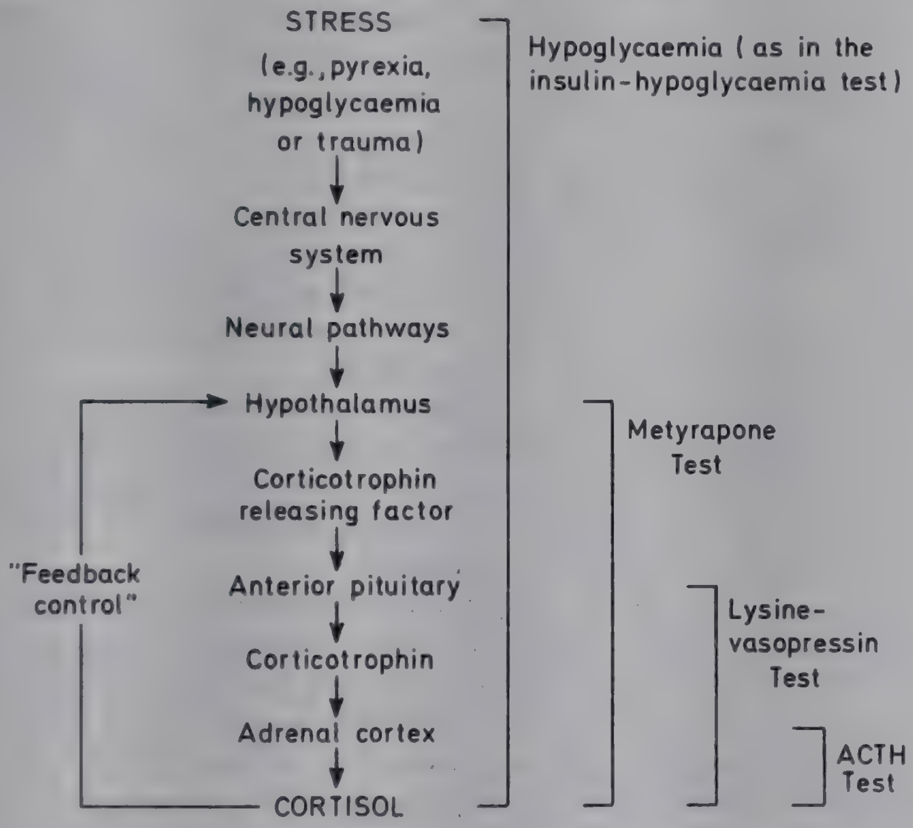


FIG. 86

Postulated sites of action of test procedures used in assessing hypothalamic-pituitary-adrenal function.

Useful information on growth hormone secretion and prolactin can be obtained from the same samples. The corticosteroid response to insulin induced hypoglycaemia is probably the most sensitive of the tests currently available for assessing hypothalamic-pituitary-adrenal function.

As shown in Figure 86, insulin induced hypoglycaemia measures the function of the entire hypothalamic-pituitary-adrenal axis. If a patient has a normal diurnal rhythm of plasma cortisol, normal response to ACTH stimulation and a normal plasma cortisol response to insulin hypoglycaemia, there is no abnormality of the hypothalamic-pituitary-adrenal axis. If adequate insulin hypoglycaemia does not give a normal rise in plasma cortisol, it is sometimes possible to localise the lesion further by proceeding to metyrapone and lysine-vasopressin tests.

Metyrapone Test. Metyrapone inhibits the enzyme 11-beta-hydroxylase that is involved in the final step in the synthesis of cortisol (Fig. 85). Its oral administration in a dose of 750 mg four-hourly for 24 hours therefore produces a fall in the secretion of cortisol which activates the hypothalamic-pituitary axis via the feed-back mechanism so that the secretion of ACTH is increased. Consequently, there is a build-up of the immediate precursor of cortisol, 11-deoxycortisol, which is released into the circulation. After being metabolised in the liver to its tetra-hydro-derivative, it is excreted in the urine in the 17-oxogenic steroid fraction. In carrying out a metyrapone test the plasma fluorigenic steroids and the 24-hour urinary 17-oxogenic steroids should be measured during the preceding 48 hours, the 24 hours during the administration of metyrapone, and the following 24 hours. If the hypothalamic-pituitary axis is normal there should be a fall in the plasma fluorigenic steroids and a rise in the urinary excretion of 17-oxogenic steroids. The latter will not occur with lesions in the hypothalamus or pituitary that affect CRF or ACTH secretion. Unlike ACTH stimulation tests, the metyrapone test cannot be done if the patient is taking exogenous corticosteroids in any form. The normal response in the urinary 17-oxogenic steroids is a mean maximum level of 36 mg/day with a range of 23-46 mg/day. The mean increment in normal subjects is 24 with a range of 11 to 39 mg/day. The metyrapone test should be avoided in pregnancy and should not be done in suspected primary adrenal failure.

Abnormal findings in the metyrapone test sometimes occur in subjects in whom the hypothalamic-pituitary-adrenal axis is normal by all other criteria; this is thought to be due to failure to achieve a sufficient block of hydroxylation in the adrenal, either because of inadequate absorption of metyrapone or because of its very short half-life in plasma.

Lysine-vasopressin Test. If the metyrapone test gives an abnormal result, one may proceed to do a lysine-vasopressin test. Lysine-vasopressin has an action similar to CRF. Normal peak values of plasma fluorigenic corticosteroids in response to 10 units i.m. at 30-60 minutes show a mean of 27 with a range of 16-45 μg/100 ml, the increment being a mean of 16 with a range of 5-39 μg/100 ml. Lysine-vasopressin causes vasoconstriction and must not be used in patients with myocardial ischaemia. The clinical value of the test is limited by the fact that a proportion of normal subjects fail to show a detectable response in either ACTH or plasma cortisol.

Pyrogen tests are highly unpleasant and are no longer warranted, comparable or better information being obtained from insulin hypoglycaemia.

3. **Measurement of ACTH Levels in Plasma.** If in the presence of low levels of plasma fluorigenic steroids, the plasma ACTH level is high, one would have strong evidence of primary adrenocortical insufficiency. The measurement of plasma ACTH levels greatly facilitates the study of hypopituitarism as it is no longer necessary to use the patient's potentially normal adrenals in an *in vivo* bioassay. Such direct measurements of ACTH are also particularly helpful in relation to insulin hypoglycaemia, metyrapone and lysine-vasopressin tests.

Treatment of Adrenocortical Insufficiency

All patients with adrenocortical insufficiency will require replacement therapy with a glucocorticoid, while the majority of patients with Addison's disease will also need a mineralocorticoid. In congenital adrenal hyperplasia, full replacement doses of glucocorticoid, and mineralocorticoid if the nature of the enzymic block demands it, will suppress ACTH secretion and prevent the excessive formation of metabolites with consequent regression of the clinical features.

Cortisol is the drug of choice for routine glucocorticoid replacement therapy. Cortisone acetate, although widely used, has the disadvantage that it has to be metabolised by the liver to cortisol before having any physiological action. Abnormal liver function results in reduced conversion of cortisone acetate to cortisol and the possibility of impaired liver function is particularly relevant in cases of secondary adrenal insufficiency who are taking oral androgen therapy for concomitant hypogonadism. Other synthetic glucocorticoids, e.g. prednisone, prednisolone, dexamethasone and betamethasone are useful in keeping a patient in good health while adrenal function tests are being done, but have the disadvantage in terms of continual replacement therapy in that they do not react in the fluorigenic corticosteroid assay of Mattingly so their dosage cannot be monitored. Cortisol, cortisone acetate and the synthetic glucocorticoids have a biological action of some six to eight hours.

For maintenance treatment it is best to give the glucocorticoid medication in a regime which mimics the normal diurnal variation of cortisol output. For most patients this would be 20 mg cortisol at breakfast time and 10 mg at about 1800 hours. The equivalent doses of cortisone acetate would be 25 mg and 12·5 mg respectively. While it is not possible to be dogmatic about how much glucocorticoid any individual may require as absorption and metabolism may vary, the regime described will meet the needs of most patients. To assess the requirements of those whose response appears to be unsatisfactory a corticosteroid profile should be carried out. Plasma fluorigenic corticosteroids should be estimated before and half an hour, one hour and then at two-hourly intervals after an oral dose of 20 mg of cortisol, or whatever dose seems to be clinically indicated. The plasma level usually reaches a peak after 30-60 minutes and the amount of cortisol should be adjusted to give a peak of 25-30 μg/100 ml and a level of about 6 μg/100 ml before the evening dose.

The maintenance dose of fludrocortisone should be adjusted according to the serum electrolytes, the state of hydration of the patient and the blood pressure. Most patients require 0·05-0·15 mg in a single morning dose. The signs of overdosage of mineralo-corticoid are those of sodium retention, i.e. hypertension, oedema, headaches and arthralgia, and also potassium depletion, hypokalaemic alkalosis and muscular weakness. The occasional patient is unable to tolerate fludrocortisone and in these cases subcutaneous or intramuscular injection of deoxycortone acetate (DOCA) in oil may be given in a dose of 2·5 mg daily or on alternate days. A long-acting preparation may be given in a single dose of 50 mg every three to four weeks, e.g. desoxycortone trimethyl acetate (DCTMA); 2·5 mg DOCA, 0·1 mg fludrocortisone daily, and 75 mg DCTMA monthly are equivalent in terms of sodium retention.

The regime to be followed in secondary adrenocortical insufficiency is the same as in Addison's disease except that a mineralocorticoid is not required as aldosterone production is little affected. Any associated condition due to lack of other trophic hormones will require therapy along the usual lines.

During periods of stress, e.g. trauma, infection, operations, it is necessary for the dosage of glucocorticoid to be increased to mimic what would happen in an individual with normal function of the hypothalamic-pituitary-adrenal axis. Thus if a patient develops a severe cold or influenza he should increase the dose of oral steroids to twice their normal maintenance level for two or three days. Should gastroenteritis with or without vomiting occur the oral glucocorticoid should be switched to intramuscular hydrocortisone at an increased dose level. Consequently, it is essential that patients with impaired adrenal function, either primary or secondary, have available ampoules of hydrocortisone hemisuccinate for injection which are not outdated and which they know how to use.

Every patient on oral steroids of whatever form should have a steroid card or preferably a bracelet giving details of the condition from which he is suffering, dosage of steroids that he is taking and the address of his physician. The opportunity should be taken when the patient is initially seen and during the hospitalisation period to indoctrinate him in the importance of carrying this means of identification everywhere, and to increase the dose of corticosteroids if he develops an infection or incurs an injury. Should the patient be involved in an accident and be taken unconscious to a casualty department the outcome may be avoidably disastrous if the information that the patient is taking steroids is not available.

Any operation, even the most minor such as a dental extraction, is a potential hazard to a patient with adrenocortical insufficiency. On no account should such a patient be given morphine or pethidine. For dental extraction the patient should be admitted to hospital for the day. It is usually only necessary to give twice the normal dose of glucocorticoid on the day of the extraction and possibly the morning following and to resume normal replacement dosage thereafter provided there are no complications. Larger doses of steroids and more careful monitoring both pre- and post-operatively are required for more major surgery.

Acute adrenal crisis is a medical emergency. If promptly treated with intravenous hydrocortisone hemisuccinate (or hydrocortisone sodium succinate) and intravenous fluids there is in most cases a rapid and dramatic improvement in a previously moribund patient over 12 to 24 hours. Occasional cases will need more protracted treatment depending upon how quickly the precipitating cause, e.g. infection, is brought under control. In incipient crises, intravenous fluids may not be necessary, but in frank crises with peripheral circulatory failure the patient may succumb in spite of massive doses of intravenous hydrocortisone. Hypertensive agents are not helpful in this situation. The intravenous fluids should consist of 5 per cent dextrose to correct hypoglycaemia and isotonic saline to correct sodium loss. Hydrocortisone hemisuccinate is best given parenterally over the first 24-48 hours until gastrointestinal symptoms settle completely and one can be sure that oral medication will be effective. The initial dose should be 100 mg intravenously six hourly for the first 24 hours and then 50 mg six-hourly for the next 24 hours. If progress is satisfactory, oral cortisol can be given thereafter in a dose of 20 mg eight-hourly. The dose of oral cortisol can then be further reduced in a stepwise fashion by 10 mg daily until normal maintenance levels are reached. Below 40 mg of oral cortisol per day a mineralocorticoid is best added to the therapeutic regime, initially in a single morning dose of 0·1 mg fludrocortisone.

Prognosis in Adrenal Insufficiency

With modern therapy the life expectancy of patients with adrenal insufficiency should be normal, within the limits imposed by any associated disease such as pituitary tumour or other clinical disorder such as diabetes mellitus which may co-exist with autoimmune adrenal insufficiency. Otherwise the main risk to life is the avoidable occurrence of acute adrenal crisis and delay in its prompt management.

Corticosteroids and ACTH in the Treatment of Disease

Extensive use has been made of the anti-inflammatory actions of corticosteroids and of their synthetic analogues since cortisone became available in 1948. Alternatively, ACTH may be administered parenterally to augment the endogenous production of cortisol. Some of the steroid analogues are listed in Table 9 with the dosage which is therapeutically equivalent to 20 mg cortisol. Of these the most commonly used for purposes other than replacement therapy, is prednisolone. It is widely prescribed in the treatment of connective tissue diseases, of autoimmune disorders and conditions involving other forms of immune reaction. Corticosteroids may be used to suppress inflammation, for example in conjunction with chemotherapy in tuberculous pericarditis to prevent the later development of constrictive pericarditis. The distinction between inflammation and immune reaction may be difficult to make. The use of corticosteroids in pharmacological doses is discussed under the heading of the various diseases for which they may be employed.

TABLE 9

Relative Potencies of Corticosteroids and their Synthetic analogues

Compound	Size of oral tablet (mg)	Approximate Relative Potency		Equivalent dosage (for anti-inflammatory effect) (mg)
		Anti-inflammatory (glucocorticoid) effect	Sodium-retaining (mineralo-corticoid) effect	
Cortisone	25	1	1	25
Cortisol	20	1·2	1	20
Prednisolone/ prednisone	5	5	0·8	5
Betamethasone	0·5	40	negligible	0.5
Dexamethasone	0·5	37	minimal	0.5
Fludrocortisone	0·1	0·05	200	—
Aldosterone*	—	none	500	—

* Not used in clinical practice.

The Dangers of Corticosteroid Therapy

The use of corticosteroids in a dosage in excess of that required for replacement therapy carries certain risks which must be balanced against the possible therapeutic advantages. These risks can be subdivided into two types: (1) the undesirable metabolic consequences that cannot be separated from the anti-inflammatory effect of the steroid and (2) the suppression of the hypothalamic-pituitary-adrenal (HPA) axis that may follow the use of pharmacological doses of steroids over a prolonged period.

The metabolic consequences are those that are encountered in Cushing's syndrome and are naturally more pronounced the higher the dose and the longer the treatment. Thus, although certain corticosteroid analogues may have slightly less mineralocorticoid activity than cortisol, fluid retention, moon face, central obesity, striae, etc., may all be induced. The glucocorticoid action not infrequently precipitates diabetes mellitus and the catabolic effect is responsible for osteoporosis as an insidious but frequent complication of long term steroid therapy. Corticosteroids may modify the normal response to a major illness so that pain, tenderness, fever or a raised ESR may be abolished, while the response to inflammation and therefore the defences against infection may be poor and healing impaired. In this way treatment with these drugs may be responsible for masking the more typical and sometimes dangerous consequences of a variety of illnesses. For example, oral corticosteroids may induce peptic ulceration with perforation without pain and the physical signs indicative of inflammation in the peritoneal cavity may not be present. As in Cushing's syndrome, mental symptoms may be troublesome, ranging from euphoria to depression which may be so severe as to lead to suicide.

The suppression of the HPA axis following prolonged corticosteroid therapy in doses greater than 7·5 mg prednisolone per day or its equivalent may be long standing, especially with regard to the hypothalamic-pituitary portion of the axis. This may make it difficult to withdraw steroids, the patient being as vulnerable as someone with secondary adrenocortical insufficiency due to organic pituitary disease. Stimulation of the adrenal cortex in such cases is usually possible with adequate ACTH dosage, but there is no known way of producing a comparably strong and prolonged stimulus to the hypothalamic-pituitary axis without risking adrenocortical failure. When trying to wean a patient off corticosteroid therapy, one should first ensure that the adrenal cortex is functional by giving tetracosactrin depot 1·0 mg i.m. on three consecutive mornings and measuring the plasma cortisol response at 30 minutes, 1 hour and 5 hours. Then, after gradually reducing the dosage of oral steroid, a maintenance dose of 20 mg cortisol should be given at 0800-0900 hours and no cortisol in the evenings; the hypothalamo-pituitary axis will then have no exogenous steroid to suppress the secretion of CRF or ACTH in the early hours of the morning. In this way a normal diurnal rhythm may be restored and the HPA axis should thereafter respond normally to stress. This may take many months to achieve, while in other cases, normal function may be restored shortly after steroid therapy has been withdrawn.

Because it can be such a difficult task to withdraw corticosteroid therapy when it has been used in pharmacological dosage for a prolonged period, attempts have been made to use synthetic ACTH preparations such as tetracosactrin depot in place of oral corticosteroids. When used in appropriate dose, there is evidence that therapeutically useful elevation in the plasma cortisol levels may be achieved without risk of suppression of the HPA axis. ACTH therapy is therefore probably better than oral corticosteroid treatment for chronic relapsing conditions when it is hoped that the steroids can be withdrawn during periods of remission. In children ACTH therapy has the distinct advantage over treatment with oral steroids in that it causes less inhibition of growth. Porcine ACTH gel should no longer be used on account of the hypersensitivity reactions that it may cause.

TABLE 10

Complications in 108 Patients with Oral Corticosteroids and 105 treated with ACTH

	Oral steroids %	Corticotrophin %
Moon face	55	50
Weight increase	27	28
Dyspepsia	54	25
Peptic ulceration	11	2
Bruising	25	4
Hypertension	17	27
Acne	8	29
Pigmentation	4	19

(From Savage *et al.* (1962), *Lancet*, **1**, 232.)

The relative incidence of complications with oral steroids compared to those with parenteral ACTH is shown in Table 10. In view of the serious risks involved in the use of corticosteroid or ACTH therapy very careful consideration must be given before they are employed and the practitioner must be convinced that the therapeutic benefits outweigh the disadvantages.

Phaeochromocytoma

Phaeochromocytomas are tumours of chromaffin tissue which secrete catecholamines, predominantly noradrenaline but also adrenaline. The tumours, most of which are benign, may occur at any site along the sympathetic chain, but 90 per cent are found in the adrenal glands. Rarely the lesions may be multiple. Phaeochromocytoma is an uncommon tumour but of considerable interest because of its pharmacological effects. The clinical presentation depends upon the relative amounts of noradrenaline and adrenaline secreted. The most common sign is hypertension which may be paroxysmal or sustained and associated with episodes of extreme skin pallor, sweating, palpitations, headache, epigastric pain and chest discomfort. Apprehension is common during a paroxysm.

The diagnosis of phaeochromocytoma rests with the demonstration of increased levels of catecholamines or their metabolites in the urine, e.g. metanephrine and normetanephrine or vanilylmandelic acid (VMA). The location of the tumour is best shown by adrenal venography.

The treatment of phaeochromocytoma is by excision. In order to avoid hypertension and arrhythmias during induction of anaesthesia and handling of the tumour at operation, the pre-operative preparation of the patient with α- and β-adrenergic blocking agents (phenoxybenzamine and practolol) is essential. Emergencies associated with hypertensive crises should be dealt with by the intravenous administration of phentolamine in doses of 5 mg.

SEXUAL DISORDERS IN THE MALE

Disabilities of this type may present in many forms. Some are due to faults arising in the mechanism of sex determination as early as conception, others to errors later in sexual differentiation of the embryo and fetus, and after birth, in sexual development. The anatomical characteristics of the male are influenced by essential hormonal factors, particularly androgen secretion. The personality and behaviour of the male are further attributes which must be considered in assessing the individual patient's needs. A few only of the more common sexual disorders occurring in the male will be discussed here.

Hypogonadism

This term is used to include failure of one or both of the main functions of the testis, namely the production of spermatozoa and the secretion of androgens. The defect may involve only impaired spermatogenesis in the seminiferous tubules of the testis, or the interstitial (Leydig) cells of the testis may also be affected so that the secretion of testosterone by these cells is reduced or abolished. If the function of the interstitial cells is defective, then tubular dysfunction is inevitable.

Aetiology. Hypogonadism may be part of the syndrome of hypopituitarism. Hypogonadotrophic hypogonadism with an apparently normal pituitary gland appears to be due to failure of the hypothalamus to secrete the appropriate gonadotrophin releasing hormones. In addition there are cases in which the anterior pituitary is intact but the testes have been destroyed or damaged. Trauma, tuberculosis, gonococcal infections, syphilis, malignant disease, orchitis as in mumps, and surgical castration are recognised causes of primary testicular failure. Maldescent or failure of descent will also lead to failure of the tubular epithelium to develop. Haemochromatosis, cirrhosis of the liver and oestrogen administration may all be associated with testicular insufficiency. The disorder may also be due to abnormalities of the sex chromosomes (p. 11). Many cases remain, however, for which an aetiological diagnosis is still not possible, and these form the majority of patients who present with infertility as their only complaint.

Clinical Features. The nature of the sequelae from failure of function of the interstitial cells depends upon the age of the patient at the time of the onset of the disease. When this occurs *before puberty* the external genitalia and the secondary sex characteristics fail to develop. In these circumstances the epiphyses of the long bones do not close at the usual age and in consequence the patient may grow to an excessive height. The typical pre-pubertal eunuch develops into a tall man with a hairless face, a high-pitched voice, small genitalia and an immature personality.

When the onset of the disease is *post-pubertal* the changes are less striking. Growth is not affected and there is regression rather than disappearance of the secondary sex characteristics. The external genitalia undergo partial atrophy. Fatigue, loss of initiative and of sexual desire (libido) are common complaints. In some patients, particularly when the deprivation is sudden as after surgical castration, there may be 'menopausal symptoms' such as hot flushes and profuse sweating, unless full replacement therapy is provided.

Treatment. Hypogonadism due to deficiency of androgens may be corrected by replacement therapy with testosterone. The most satisfactory and economical form of therapy is the implantation of 600 mg of testosterone, in the form of 3-5 pellets, into the subcutaneous tissue of the anterior abdominal wall. Such an implant is gradually absorbed over a period of six to eight months, after which it may be renewed. Alternatively fluoxymesterone, a synthetican alogue of testosterone, can be given by mouth in doses of 10-20 mg daily.

In some cases of deficiency of the germinal epithelium, especially when this is due to a lack of gonadotrophin, increased spermatogenesis may be achieved by treatment with Clomiphene (p. 674).

Cryptorchism

Cryptorchism (undescended testis) is due to an anomaly of the pathway of descent which occasionally may be surgically remediable. Highly retractile testes, particularly in an obese boy, may be mistaken for cryptorchidism. Carcinoma is more common in undescended than normal testes. If the glands remain in the inguinal canal they are more liable to trauma than if situated in the scrotum. The seminiferous tubules will fail to develop in an undescended gland, and if the condition is bilateral, sterility will follow. Even in testes which remain undescended into adult life the interstitial cells function normally, so that the secondary sex characters develop in the usual way.

A course of chorionic gonadotrophin, 4000 i.u. thrice weekly for a month, should be given at about six years of age. If this is unsuccessful the testis or testes should be placed in the scrotum surgically.

Impotence

Impotence, that is inability of the male to have sexual intercourse, is due to psychological causes in the majority of cases, and in these circumstances is not due to abnormality of the testes. Rarely it may be an important early symptom in organic diseases such as diabetes mellitus, disseminated sclerosis and tabes dorsalis. In hypogonadism due to anterior pituitary deficiency, a complaint of impotence is unusual; such patients usually have little interest in sexual function, and are unlikely to make this complaint spontaneously until they have received treatment for adrenal and thyroid insufficiency. They may then become aware of their impotence and require treatment with an androgen, e.g. testosterone and gonadotrophins should they wish to become fertile.

Infertility in the Male

Sterility in the husband is believed to be responsible for the infertility of approximately one-third of all childless marriages. The cause is usually defective development of the germinal epithelium in the seminiferous tubules, with oligospermia or azoospermia, but may follow hypogonadism due to any of the causes described earlier.

Treatment of a varicocele has sometimes corrected infertility. Obstruction of the vas deferens may also be amenable to surgery. Chromosomal abnormalities may be recognised by examination of a buccal smear for Barr bodies, but usually confirmation requires a full karyotype analysis (p. 3). Seminal analysis is a simple procedure and a low sperm count, or the presence of abnormal and immotile forms may be detected in this way. Testicular biopsy frequently provides valuable information on the development of the spermatic tubules and on the maturation of the germinal epithelium. This investigation should be undertaken before declaring a hopeless prognosis since the use of clomiphene for a period of six months or longer as a means of promoting gonadotrophin secretion, may occasionally stimulate spermatogenesis.

DISORDERS OF SEXUAL DETERMINATION AND DIFFERENTIATION

As already stated the mechanisms responsible for full sexual development and function are complex, and may fail in many ways at different stages in either sex. Abnormalities of the sex chromosomes of the germ cells or of the zygote are frequently associated with failure of sexual development, in such a way that in many cases the individual affected may show some of the characteristics of both sexes. The term 'intersex' is now preferred to describe this group of patients. True hermaphroditism occurs much less commonly than the intersexes; the former term is reserved for patients in whom male and female gonadal tissue is found to co-exist.

DISORDERS OF THE MENOPAUSE

The term menopause is used to describe the cessation of the menstrual cycle, which occurs in most women between the ages of 45 and 50, abruptly or gradually, and as a direct result of the failure of the ovaries to produce oestrogens and progesterone. As a consequence of this failure the pituitary gland becomes more active and produces gonadotrophic hormones in greater quantity. Assays for these substances may be of value in distinguishing amenorrhoea due primarily to failure of the ovaries from amenorrhoea due to failure of the pituitary to secrete gonadotrophins.

Clinical Features. The ease with which a woman adapts herself to the change of circumstances associated with the menopause varies widely. In some women the loss of reproductive capacity is associated with depression and other psychological symptoms; in others adjustment is readily achieved and may be unattended by any emotional reaction. In the group of patients who are troubled by symptoms, nervousness, emotional instability, irritability, insomnia, tremor and particularly hot flushes and cold sweats are common complaints. Depression is common and occasionally may be severe with suicidal tendencies. The thyroid may be palpably enlarged and frequently it is difficult to be certain on clinical grounds alone whether the symptoms present are due to a mild degree of hyperthyroidism or to the menopause. Obesity may first appear, or, if previously present, may increase at this time. Hirsutism, especially the appearance of dark hair on the upper lip and chin, is not uncommon and may be sufficiently pronounced to require treatment for cosmetic reasons. Osteoarthrosis may be responsible for considerable disability, particularly in the obese (p. 786). Osteoporosis commonly presents for the first time in the early years after the menopause (p. 144).

Pruritus vulvae is a common complication which is frequently associated with atrophic changes in the mucous membranes of the genital tract. Leukoplakia vulvae may develop, and if untreated may progress to carcinoma. Senile vaginitis, which not infrequently occurs, may cause considerable distress from irritation, dysuria and vaginal discharge, especially if complicated by secondary infection.

Treatment. The essential treatment is explanation of the nature of the condition, coupled with specific treatment for the complications. Tranquillisers may occasionally be helpful. Features attributable to oestrogen deficiency call for replacement therapy. The synthetic oestrogens are active when given by mouth and of these the most powerful is ethinyl oestradiol. The daily dose required to suppress menopausal symptoms in different individuals varies from 0·01 to 0·1 mg of ethinyl oestradiol; this should be given in courses lasting for 21 days, repeated if necessary after an interval of 7 days. The patient must be warned that treatment in this way can be expected to be followed by vaginal bleeding as in a normal menstrual period.

Other appropriate measures, such as dietary control of obesity and local treatment of arthritis, may also be required. Excessive growth of hair on the face may be removed by shaving or depilatory cream, or may be made less conspicuous by bleaching with hydrogen peroxide. Depression complicating the menopause responds well to psychiatric treatment.

W. J. IRVINE.
J. A. STRONG.

'Imp

DIABETES MELLITUS

Diabetes mellitus is a clinical syndrome characterised by hyperglycaemia, due to deficiency or diminished effectiveness of insulin. The disease is chronic and affects the metabolism of carbohydrate, protein, fat, water and electrolytes, sometimes with grave consequences. The metabolic derangement is frequently associated with permanent and irreversible functional and structural changes in the cells of the body, those of the vascular system being particularly susceptible. The changes lead in turn to the development of well-defined clinical entities, the so-called 'complications' of diabetes, which most characteristically affect the eye, the kidney and the nervous system.

Incidence. Diabetes mellitus is the most common of the endocrine disorders. The prevalence in this country is over 1 per cent of the population, although about half of those affected are unaware of the fact and may remain undetected.

Aetiology

On the basis of aetiology two main types of diabetes are recognised, namely primary (idiopathic) diabetes and secondary diabetes.

Primary (Idiopathic) Diabetes

The great majority of cases seen belong to this group. Although several contributing factors are known to be involved, the precise aetiology is still uncertain.

Heredity. A familial tendency to diabetes undoubtedly exists but neither the specific biochemical defect nor its mode of inheritance has yet been identified. Genetic factors are probably more important in those who develop diabetes before the age of 40, but in both young and old, environmental and other factors also operate and may determine which of those with a genetic predisposition actually develop the clinical syndrome, and when this occurs.

Age. The disease may appear at any age, but 80 per cent of cases occur after the age of 50, and the highest incidence of new cases is in the 60 to 70 age group. Diabetes is therefore principally a disease of the middle-aged and elderly.

Sex. There are rather more young male diabetics than female; in middle age women are more often affected. Pregnancy and increasing parity may add to the likelihood of developing diabetes.

Obesity. The association of obesity and diabetes has long been recognised, but it is still uncertain whether obesity is the result or the cause of diabetes. The majority of middle-aged diabetic patients are obese, but only a minority of obese people develop diabetes.

Infections. These may unmask latent diabetes. Staphylococcal infections in particular are frequently associated with the development of clinical diabetes.

Stress. Either physical injury or emotional disturbance is sometimes suggested as the initial cause of the disease, just as in many other diseases that arise mysteriously and unexpectedly. However, since corticosteroid administration or ACTH therapy may be associated with the development of clinical signs of diabetes, and since surgical operations and severe infections appear to precipitate the disorder, stress, in so far as it elicits an adrenocortical response, must be regarded as a factor of importance. A severe stress, such as a car crash, does not cause diabetes in people who would otherwise never have had it, but it may change a latent form of the disease into clinical diabetes.

Secondary Diabetes

A minority of cases of diabetes occur as a result of a recognisable pathological process or secondary to the treatment of some other condition.

1. In *pancreatic diabetes* the pathological disorder causes destruction of the pancreas and leads to impaired secretion and release of insulin. For example, ① pancreatitis, ② haemochromatosis and ③ carcinoma of the pancreas can all cause diabetes; diabetes will also follow ④ pancreatectomy.

2. In another group of cases, diabetes occurs because there are abnormal concentrations of hormones in the circulation which are insulin antagonists.

(*a*) Administration of *growth hormone* can produce permanent diabetes in experimental animals and about 30 per cent of patients with acromegaly are diabetic.

(*b*) *Adrenocortical hormones*, such as cortisol, raise the concentration of glucose in the blood by increasing protein breakdown and by inhibiting utilisation of glucose by the peripheral tissues. Thus, many patients with Cushing's syndrome show impaired carbohydrate tolerance; conversely increased sensitivity to insulin is an important feature of Addison's disease and of hypopituitarism, and this can be corrected by the administration of corticosteroids.

(*c*) *Adrenaline* raises the blood glucose concentration by increasing the breakdown of liver glycogen and by suppressing the secretion of insulin. Patients with phaeochromocytoma frequently show a diabetic blood glucose curve on glucose tolerance testing and the incidence of these uncommon tumours is relatively high among diabetic patients.

(*d*) *Thyroid hormone* in excess will aggravate the diabetic state and some patients with hyperthyroidism show impaired glucose tolerance.

(*e*) *Gestational diabetes* refers to the hyperglycaemia which can occur temporarily during pregnancy in individuals who have an inherited liability to develop the disorder. During normal pregnancy there is an increased production of hormonal antagonists to insulin, which in turn demands an increased rate of secretion and release of insulin. A failing pancreas may be unable to meet this demand.

3. Various forms of therapy may precipitate *iatrogenic diabetes* in those genetically susceptible. For example, diabetes can occur as a result of the therapeutic administration of corticosteroids; certain diuretics, particularly the thiadiazine group, can also have a diabetogenic effect.

4. *Liver disease*, particularly cirrhosis and hepatitis, may be associated with impaired glucose tolerance.

Chemical Pathology

Although it has already been emphasised that diabetes is a clinical syndrome combining several different pathological processes in a common clinical picture, it can be asserted that in every case the hyperglycaemia results from the fact that the insulin secreted by the pancreas is either insufficient in amount or ineffective in action for one or more reasons. In any event increased gluconeogenesis and lipolysis will follow as compensatory reactions under the influence of such hormones as growth hormone and adrenocortical hormones, in what is basically a situation of glucose lack. Thus the hyperglycaemia characteristic of diabetes arises from two main sources, namely a reduced rate of removal of glucose from the blood by the peripheral tissues and an increased rate of release of glucose from the liver into the circulation. Although significant amounts of insulin can be detected in the plasma of some cases of primary diabetes, the majority of cases presenting spontaneously with classical symptoms of diabetes are characterised, prior to treatment, by a marked absolute deficiency of plasma insulin when compared with normal subjects. Moreover the level of plasma insulin correlates well with the clinical picture and the type of treatment subsequently required. It seems most likely that the abnormalities in carbohydrate tolerance and lipid metabolism result directly from the lack of insulin. However, the sequence of events which culminates in the development of this insulin-deficient state is still uncertain. There are two possibilities: either diabetes is primarily a disorder of the insulin-secreting mechanism; or else the primary defect is outside the pancreas, in the form of either a circulating antagonist to insulin or a cell-based resistance to the action of insulin, with deficiency of insulin occurring secondarily.

Consequences of Hyperglycaemia and Glycosuria. When the glucose concentration in the blood exceeds the capacity of the renal tubules to reabsorb it from the glomerular filtrate, *glycosuria* occurs. In the majority of people the level of blood glucose at which this happens is approximately 180 mg/100 ml. Glucose increases the osmolality of the glomerular filtrate and thus prevents the reabsorption of water as the filtrate passes down the renal tubular system. In this way the volume of urine is markedly increased in diabetes and *polyuria* and *nocturia* occur. This in turn leads to loss of water and minerals which results in *thirst* and *polydipsia*. In acute cases, or in more slowly progressive cases where the condition remains undetected for a long period of time, and particularly if the fluid intake has been low because of mental confusion or for other reasons, severe depletion of water and electrolytes may occur. As the concentration of glucose in the blood rises the extracellular fluid becomes hypertonic, and water leaves the cells. In the early stages, before the volume of the extracellular fluid is grossly reduced the patient will show relatively few clinical signs, but if the loss of water and electrolytes continues, depletion of extracellular fluid will occur, with the development of the clinical features of severe dehydration.

Consequences of Poor Glucose Utilisation. Impaired utilisation of carbohydrate results in a sense of *fatigue*, and causes two main compensatory mechanisms to operate in an attempt to provide alternative metabolic substrate. Both of these lead to loss of body tissue, that is *wasting*, which may occur in spite of a normal or even an increased intake of food, and which is additional to any loss of weight resulting from loss of body fluid.

1. INCREASED GLYCOGENOLYSIS AND GLUCONEOGENESIS. Glycogen and protein are present in cells associated with water and intracellular electrolytes. As glycogen and protein are catabolised, glucose, nitrogen, water and electrolytes, particularly potassium, are released into the extracellular space. An increased urinary excretion of potassium, magnesium and phosphorus therefore occurs in uncontrolled diabetes.

2. INCREASED LIPOLYSIS. This is seen as a raised fasting plasma concentration of non-esterified fatty acid (NEFA), and a diminished fall in plasma NEFA in response to a carbohydrate load. The extent to which increased lipolysis occurs is proportional to the degree of insulin deficiency. If the latter is marked, the normal response to feeding, namely suppression of lipolysis, may be completely lost and the plasma concentration of NEFA may remain consistently elevated to three or four times the normal level.

Fatty acids are taken up by the liver and degraded through eight steps within the mitochondria of the liver cells. Each stage yields one molecule of acetyl coenzyme A. Normally most of these molecules enter the citric acid cycle by condensing with oxaloacetic acid, but in severe diabetes more is formed than can enter the citric acid cycle. Instead acetyl coenzyme A is converted to acetoacetic acid. Most of this is then reduced to beta-hydroxybutyric acid, while some is decarboxylated to acetone. These *ketone bodies*, when formed in small amounts, are usually oxidised and utilised as metabolic fuel. However the rate of utilisation of ketone bodies is limited. When the rate of production by the liver exceeds that of removal by the peripheral tissues, then the blood level rises. Ketone bodies raise the osmolality of the plasma and so also lead to the withdrawal of water from the cell. They are strong acids which dissociate readily and release hydrogen ions into the body fluids. The fall in pH is reduced by the buffers of the blood; the most important being bicarbonate. The dissociation of carbonic acid is reduced, and the ratio of bicarbonate ions to carbonic acid falls, and measurement of plasma bicarbonate will show a lower value than normal. This state is called *keto-acidosis*. The fall in pH and increase in P_{CO_2} in the arterial blood stimulate pulmonary ventilation so that clinically *hyperpnoea* or 'air hunger' is observed.

The extent to which the clinical features of dehydration and ketoacidosis are seen in the individual case will depend on such factors as the speed at which the condition develops and the extent to which the patient himself increases his intake of fluid, as well as on the degree of insulin deficiency present.

Morbid Anatomy

The Pancreas. Histological examination of the pancreas at necropsy shows abnormalities in the islets of Langerhans in most cases of clinical diabetes. However it should be noted that these abnormalities are mostly of a quantitative nature and nearly all the types of lesion in the islets in diabetes can also occur in non-diabetics, although the lesions are much less common in the latter.

In the younger age group, that is those under the age of 40, the majority of whom require treatment with insulin, marked changes can be seen in the islet tissue of the pancreas which, regardless of the primary cause of diabetes, is sufficient in itself to account for the disease. The abnormality consists essentially of the degeneration of the islet tissue, from which the beta cells have largely disappeared, leaving behind a variable number of alpha cells and a majority of small undifferentiated cells. The remaining beta cells show evidence of excessive activity; the nuclei are commonly enlarged with degranulation of the cytoplasm. These appearances of the pancreas are consistent with the fact that most young diabetics have extremely low plasma insulin levels when first seen.

In the middle-aged and elderly, the majority of whom do not require treatment with insulin, the moderate reduction in the total mass of islet tissue which is commonly seen does not appear to be sufficient in itself to account for the degree of impaired carbohydrate tolerance shown by many of these patients. On the other hand, the observation that in many cases the beta cells, despite prolonged hyperglycaemia and their reduced number, fail to develop cytological signs of hyper-activity, suggests that in these diabetics the beta cells may be relatively insensitive to the stimulus of an elevated blood glucose. Failure to respond to hyperglycaemia could result from vascular lesions or from alterations in the islet stroma, interfering with the exchange between the blood and the islet cells. Fibrosis, hyalinisation, and fibrin deposits in the pericapillary space and alterations in the islet epithelial basement membrane are frequently present in older diabetics.

Extra-pancreatic Tissues. Long-standing diabetes is commonly associated with a general disorder of small blood vessels which is seen as an abnormal thickening of the basement membrane of the capillaries throughout the body. It is uncertain whether this occurs in the pre-diabetic period, but its development thereafter seems to be mainly related to the duration of clinical diabetes. Thickening of the basement membrane *per se* is not pathognomonic of diabetes. It occurs for example as part of the normal ageing process; however the increased permeability of the thickened basement membrane in diabetes is a unique pathological feature. The widespread involvement of small blood vessels appears to be the common denominator of the complications associated with long-term diabetes. The main clinical and pathological impact of this micro-angiopathy is to be found in the retina, the kidney and the nervous system.

Clinical Features

Clinical Types. Two main types of diabetes have long been recognised, and it is now clear that the level of plasma insulin correlates well with the clinical picture and the type of treatment subsequently required.

✓1. The *juvenile-onset type* usually develops during the first 40 years of life in patients of normal or less than normal weight. The majority develop severe symptoms of diabetes acutely, over a period of several weeks or months and if treatment with insulin is withheld they rapidly develop fatal keto-acidosis. Since administration of insulin is required for their survival, an alternative and preferable name for this group of patients is *insulin-dependent*.

✓2. The *adult or maturity-onset type* usually appears in middle-aged or elderly patients who are often obese and in whom hyperglycaemia can usually be controlled by dietary means alone or, if not, by an oral hypoglycaemic compound. For this reason it is sometimes described as the *insulin-independent type*. Insulin is detectable in the plasma of nearly all patients in this category, and they are therefore less prone to develop ketosis. In this sense the disease is less severe than in the juvenile-onset type; however, the complications associated with long-term diabetes occur in both types. Many patients with maturity-onset diabetes have a long history of mild symptoms which may come and go, and which may frequently be ignored or misdiagnosed for years before the true diagnosis is made.

Apart from patients with established clinical diabetes, two other categories are recognised.

Potential diabetics are persons with a normal glucose tolerance test who nevertheless have an increased liability to develop diabetes for genetic reasons, e.g. the children of two diabetic parents; the children of parents where one is diabetic and the other has a first degree relative who is diabetic; the non-diabetic members of pairs of identical twins where one is known to be diabetic.

Latent diabetics are persons in whom the glucose tolerance test is normal, but who are known to have given an abnormal result under conditions imposing a burden on the pancreatic beta cells, e.g. during pregnancy, infection or other severe stress, mental or physical, during treatment with cortisone or other diabetogenic drugs, or when overweight.

Symptoms and Presentation. Diabetes may be discovered in one of several ways:

1. Many patients are first noted to have glycosuria in the course of some routine examination, for insurance, for employment purposes, or pre-operatively. They may have had few or no symptoms, and no abnormal physical signs may be found.

2. Some patients present complaining of some or all of the classical symptoms of diabetes including thirst, polydipsia, polyuria, nocturia, tiredness, loss of weight, white marks on clothing, pruritus vulvae or balanitis, a change in refraction usually in the direction of myopia, paraesthesiae or pain in the limbs and impotence.

3. Diabetes may first present as a fulminating keto-acidosis associated with an acute infection or even without evidence of a precipitating cause, and in such cases epigastric pain and vomiting may be the presenting complaints. This is more likely to occur in the juvenile-onset type and such cases are acute medical emergencies.

4. Finally, patients may present complaining of symptoms due to one of the complications of diabetes, for example failing vision; paraesthesiae in the limbs or pain in the legs due to diabetic neuropathy or to peripheral vascular disease, or to a combination of the two; impotence; infection of the skin, lungs, or urinary tract. Many of these patients will also admit to symptoms attributable to glycosuria.

It should be noted that the severity of many of the classical symptoms of clinical diabetes, particularly thirst, polyuria, nocturia, pruritus vulvae or balanitis, and white marks on clothing are directly related to the severity of glycosuria. If relatively mild hyperglycaemia has developed slowly over many years the renal threshold for glucose will rise, glycosuria may be slight, and the symptoms of diabetes correspondingly trivial.

Physical Signs. Those elicited will depend very much on the mode of presentation. Cases without complications will usually show no abnormal physical signs attributable to diabetes. In some cases vulvitis or balanitis may be found, since the external genitalia are especially prone to infection by fungi (monilia) which flourish on the skin and mucous membranes contaminated by glucose. In the fulminating case the most striking features are those of dehydration, with a loose dry skin which lifts in folds, and a dry furred tongue with cracked lips causing difficulty in articulation. The intra-ocular pressure may be obviously reduced. A rapid pulse and a low blood pressure may then be anticipated. Breathing may be deep and sighing in the acidotic patient; the breath is usually foetid and the sickly sweet smell of acetone may be noticeable. Mental apathy and confusion may be present or there may be stupor or even coma.

Evidence of complications of diabetes may be noted. Ophthalmoscopy may show the typical appearances of diabetic retinopathy (p. 704). The most constant early signs of diabetic neuropathy are depression or loss of the ankle jerks, and impaired vibration sense in the legs; other abnormalities are found less commonly on neurological examination (p. 706).

The presence of diabetic nephropathy may be indicated by proteinuria in addition to glycosuria, and rarely the other features of the nephrotic syndrome (p. 595) may be apparent.

Potential and latent diabetics may complain of no symptoms and there may be no abnormality detectable on examination. However certain features are recognised as being characteristic of potential diabetes without necessarily implying that individuals who show these features will progress inevitably to clinical diabetes. For example it has been demonstrated that genetically constituted potential diabetics are predisposed to coronary arterial and peripheral vascular disease. They may show abnormal lipid patterns in response to oral contraceptives. They have a high incidence of still-born babies, abnormally large and heavy babies and babies with congenital defects. They may be much overweight at a time when there is no detectable abnormality in terms of carbohydrate intolerance.

Diagnosis. By definition hyperglycaemia remains the *sine qua non* of the clinical diagnosis of diabetes mellitus. In the individual case when the classical symptoms are present, the diagnosis is often beyond reasonable doubt by the time the history taking and physical examination are complete, and it may then be confirmed by the finding of marked glycosuria, with or without ketonuria, and a random blood sugar greater than 250 mg/100 ml. However in many cases, particularly those with diabetes of later onset who have few if any symptoms, and where glycosuria is frequently discovered by chance, the diagnosis is less obvious and a glucose tolerance test will be required.

URINE TESTING. *Glycosuria.* For individual screening purposes sensitive and glucose-specific dip-stick methods are available. Clinistix (Ames & Co.) consists of a paper stick impregnated with an enzyme preparation which turns purple when dipped in urine containing glucose. No other urinary constituent gives this reaction: it therefore provides a rapid and specific qualitative test for glucose. A positive response indicates that the urinary glucose concentration exceeds 10-20 mg/100 ml, but does not measure the amount accurately. Semi-quantitative measurement of urinary reducing activity can be obtained using copper reduction methods, most conveniently with the Clinitest tablet (Ames & Co).

When Clinitest tablets only are used to detect reducing substances in the urine, it may be necessary to establish the identity of the urinary reducing agent. Glucose can easily be identified with Clinistix. Other reducing substances, however, occasionally occur in urine, including lactose, which may be found in the later stages of pregnancy or during lactation. Pentosuria, fructosuria and galactosuria may all occur as manifestations of rare genetic disorders and special methods are required for the identification of these reducing substances when they occur in urine.

It is common practice to examine overnight specimens of urine for glucose. By using such a procedure the milder cases of diabetes will be overlooked. If a sample collected during the two hours following a meal is examined, then more of the milder cases will be recognised. There is at present no comparably simple procedure which in the individual case is of so much value in indicating the presence of grosser degrees of hyperglycaemia as testing the urine for sugar. The most serious disadvantage in the use of the urine test diagnostically arises from individual variations in renal threshold, so that on the one hand some undoubtedly diabetic people have a negative urine test for glucose due to a raised renal threshold, and on the other those with a low renal threshold give a false positive test. In order to distinguish cases of this type from patients with mild diabetes, suitable tests of carbohydrate tolerance are required.

Detection of Ketone Bodies in Urine. The amounts of ketone bodies normally excreted by healthy persons are not detected by routine side-room methods, but clinically important amounts can be detected by the nitroprusside reaction which is conveniently carried out using Acetest tablets or Ketostix test papers (Ames & Co.). Ketonuria may be found in normal people who have been fasting for long periods, who have been vomiting repeatedly or who have been eating a diet very high in fats and low in carbohydrate. Ketonuria is therefore not pathognomonic of diabetes, but if both ketonuria and glycosuria are found, the diagnosis of diabetes is practically certain.

RANDOM BLOOD SUGAR. In many cases the clinical diagnosis of diabetes can be made with the help of a single blood sugar estimation, which may be used as the final confirmatory test when the classical symptoms strongly suggest the diagnosis. In these circumstances a random blood sugar exceeding 250 mg/100 ml is almost certain to indicate diabetes. However, a random blood sugar below this level does not exclude diabetes, and in this case some degree of standardisation of the conditions under which the blood sugar is measured is necessary. In practice, the oral glucose tolerance test is the cornerstone of the diagnosis of diabetes unless a grossly elevated single blood sugar measurement, with or without clinical symptomatology, has already made this clear.

THE ORAL GLUCOSE TOLERANCE TEST (Fig. 87). The patient, who should have been on an unrestricted carbohydrate intake of at least 250 g for three days or more, fasts overnight. Out-patients should rest for at least half an hour before starting the test, and should remain seated and refrain from smoking during the test. A sample of blood is taken to measure the fasting blood glucose level and 50 g glucose dissolved in about 200 ml of water is then given by mouth. Thereafter samples of blood are collected at half-hourly intervals for two hours, and their glucose content is estimated.

The WHO Committee on Diabetes (1965) recommended that the following levels of glucose, either fasting or two hours after the glucose load, should be accepted as normal or diabetic respectively.

	Glucose concentration mg/100 ml	
Sample	Normal	Diabetic
Venous blood	<110	>130
Capillary blood	<120	>140
Plasma	<135	>155

Intermediate readings call for scrutiny of the curve as a whole and further evaluation of the patient, including the history obtained. It may be necessary to keep the patient under observation and to repeat the test at a later date should further developments occur.

The particular method of estimating the blood sugar and the precise technique used for carrying out the glucose tolerance test should be taken into account. In elderly persons and in patients after myocardial infarction or with malignant disease, blood glucose concentrations may be somewhat higher than those quoted above, without the patient necessarily having diabetes.

Differential Diagnosis of Glycosuria

1. *Renal Glycosuria*. Apart from diabetes, the commonest cause of glycosuria is renal glycosuria. If glucose regularly and consistently appears in the urine when the blood level is less than 180 mg/100 ml the individual is said to have a low renal threshold for glucose, or renal glycosuria. This is a benign condition which may run in families and which commonly occurs temporarily in pregnancy, due probably in this case to an increase in the glomerular filtration rate. Renal glycosuria is unrelated to diabetes, and is not accompanied by the symptoms of glycosuria in diabetes, i.e. thirst and polyuria, although pruritus vulvae and even ketonuria may occur.

Renal glycosuria is a much more frequent cause of glycosuria than diabetes in young persons, particularly in the age group 20 to 30 years, when they are commonly examined prior to entering the armed services, professions and industry. In the older age groups the reverse holds, and hyperglycaemia in excess of 200 mg per 100 ml can occur without any glycosuria. For this reason if urine tests for glucose are used as a method of screening for diabetes, some cases will be missed, so that a glucose tolerance test or at least a single blood glucose estimation two hours after an oral dose of 50 g of glucose should be used whenever possible.

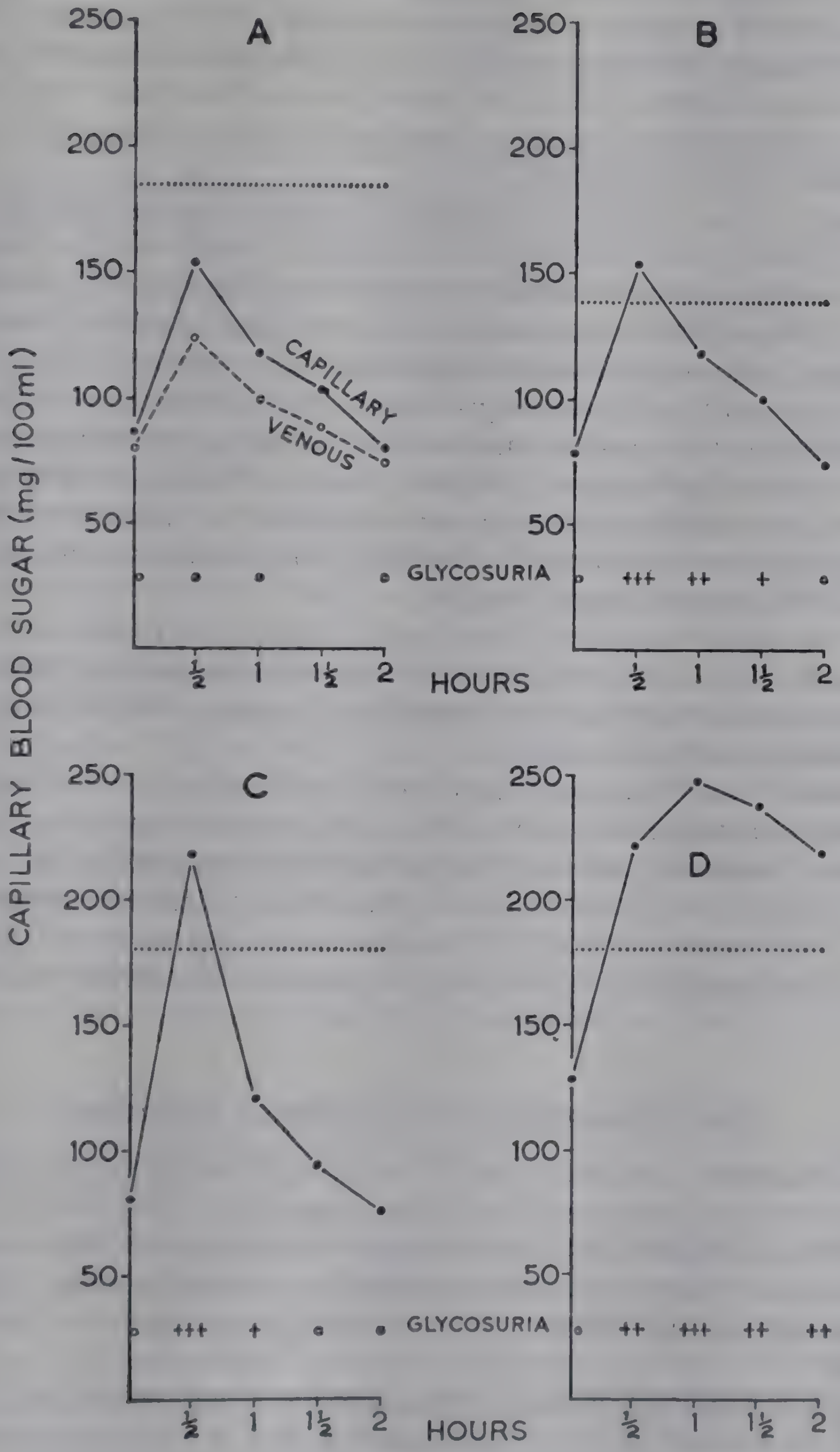


FIG. 87

The Glucose Tolerance Test: blood glucose curves after 50 g glucose by mouth, showing (A) normal curve, (B) renal glycosuria, (C) alimentary (lag storage) glycosuria and (D) diabetes mellitus of moderate severity.

It may be important to determine the renal threshold for glucose, and this can be done reliably only by testing samples of urine for glucose taken at intervals of half an hour in the course of a glucose tolerance test and relating the results to the blood glucose concentration. This information may be specially important in the occasional diabetic with a low renal glucose threshold who, if attempts are made to control his diabetes on urine tests alone, is likely to be kept in a persistent state of hypoglycaemia.

2. *Alimentary* (*Lag Storage*) *Glycosuria*. In some individuals an unusually rapid but transitory rise of blood glucose follows a meal and the concentration exceeds the normal renal threshold; during this time glucose will be present in the urine. This response to a meal or to a dose of glucose is traditionally known as 'lag storage', although alimentary glycosuria is a better term; it is not uncommon as a cause of symptomless glycosuria. It may occur in otherwise normal people or after a partial gastrectomy, when it is due to rapid absorption, or in patients with hyperthyroidism or hepatic disease. This type of blood glucose curve is usually regarded as benign and unrelated to diabetes; although the peak blood glucose is abnormally elevated, the value two hours after oral glucose is within normal limits (Fig. 88).

4. *Other Metabolic Disorders*. Impaired carbohydrate tolerance with associated glycosuria may occur with any of the forms of secondary diabetes.

5. *Raised Intracranial Pressure*. A cerebral tumour, haemorrhage or injury may be associated with glycosuria.

6. *Starvation*. Carbohydrate deprivation can lead to the development of a diabetic type of blood glucose curve with associated glycosuria in normal people. It would seem, however, that the daily carbohydrate intake has to be less than about 50 g before it has a notable effect. This effect of a low carbohydrate intake may be of importance clinically in relation to the diagnosis of diabetes in a person on a reducing diet or in acutely ill patients with a low daily intake of food.

The Management of Diabetes Mellitus

Aims of Treatment. Diabetic patients no longer die in keto-acidosis in any number, but the major problem which has emerged is the chronic invalidism of many of those whose duration of life has been extended. They live for many years with vascular disease such as cerebral atherosclerosis, coronary insufficiency and peripheral vascular disease, with renal disease and with serious visual impairment.

The ideal treatment for diabetes would allow the patient to lead a completely normal life, to remain not only symptom-free but in positive good health, to achieve a normal metabolic state, and to escape the complications associated with long-term diabetes.

Although the relationship between the degree of control and the development of serious diabetic complications is not a simple one, it would appear that vascular abnormalities are secondary to the metabolic abnormalities occurring in diabetes, since they are found in both primary and secondary diabetes and can be produced experimentally in animals rendered diabetic by various methods. It is therefore incumbent on all those who are involved in looking after diabetic patients to strive in every way to achieve as good control as is practicable in terms of blood glucose concentration, for lack of any better index at the present time.

Bearing these general principles in mind the immediate aims of treatment are therefore:

1. The abolition of symptoms of diabetes while avoiding hypoglycaemia.
2. The correction of hyperglycaemia and glycosuria.
3. The attainment and maintenance of an appropriate body weight.

The patient should realise as early as possible that it is upon him that success or failure will depend. The doctor can only advise. As adherence to a diabetic regimen demands from the patient self-discipline and a sense of purpose, every effort should be made to ensure that he understands the object of each aspect of his management. Accordingly, time must be spent on the education of the individual patient, and the doctor must be responsible for ensuring that his diabetic patients are educated to the limit of their abilities and that as far as possible they have adjusted adequately to their condition and have sufficient knowledge to undertake the day-to-day management of their diabetes competently.

As soon as the diagnosis is certain the patient should be told that he has diabetes, he should be reassured, and instruction and treatment begun forthwith. The average patient suffers from an acute anxiety reaction on being told that he has diabetes. If he understands what is wrong with him, why he has certain symptoms, and what he must do to correct the abnormalities present, it will be found that he is much less afraid and much more co-operative in carrying out the regime prescribed.

Types of Treatment. There are three methods of treatment and each involves an obligation for the patient to adhere to a dietary regimen for the remainder of his life.

1. Diet alone.
2. Diet and oral hypoglycaemic drugs.
3. Diet and insulin.

Approximately 50 per cent of new cases of diabetes can be controlled adequately by diet alone, about 20 per cent require insulin and another 30 per cent will need an oral hypoglycaemic drug. The principles governing the choice of therapeutic regimen when a diabetic patient is seen for the first time are discussed on page 695. A patient may pass from one group to another temporarily or permanently.

Diet

General Principles. The treatment of all diabetic patients, especially those who require insulin, involves some dietary restrictions if control is to be satisfactory. By regulating the amount and the times of food intake, particularly the carbohydrate intake, and by dove-tailing the dose of insulin, or of oral hypoglycaemic agent, an attempt is made to achieve a flat profile of glycaemia throughout the day and night. It is obvious that if the intake of food varies from day to day it is impossible to work out a steady insulin or other regime to cover it. It is extremely important that patients should understand that this is the main reason for dietary restriction. Many have the mistaken idea that the main purpose of dietary measures in their treatment is the avoidance of certain types of food which are 'bad'.

If one is to achieve a fixed daily intake and avoid the monotony of a static diet sheet, some kind of exchange system is necessary, and this is the basis for the construction of nearly all diets in use today. Many doctors are intimidated by the number and variety of diet sheets published and feel that, since they are not trained dietitians, they cannot treat diabetes. A dietitian is certainly most helpful but is not indispensable; the basic principles of an exchange system of dietary treatment are simple, although the education of a patient in their use is time-consuming.

The first step in preparing any dietary regimen is to map out a time-table of the patient's day including a description of his usual meals. This is an essential step and one which is too often omitted. The total daily requirement of calories must next be decided. The diet must be nutritionally adequate for the patient's needs, and it must, therefore, be estimated for each individual patient after considering such factors as age, sex, actual weight in relation to desirable weight (Table 18, p. 1007), activity, occupation, and financial resources. An approximate range for the various groups might be (1) an obese, middle-aged or elderly patient with mild diabetes, 1,000-1,600 kcal daily, (2) an elderly diabetic but not overweight, 1,400-1,800 kcal daily, (3) a young, active diabetic, 1,800-3,000 kcal daily. The importance of maintaining the body weight at or slightly below the ideal for the patient's height cannot be over-emphasised. Thus the calorie range of group 2 may have to be extended if it is not sufficient to maintain weight, and young patients in group 3 who are overweight may have to reduce their daily intake to below 1,800 kcal, perhaps temporarily.

Next the proportion of calories derived from carbohydrate, protein and fat must be allocated. The approximate ratio in British diets is, protein 12 per cent, fat 38 per cent and carbohydrate 50 per cent. The percentage of calories derived from carbohydrate should usually be reduced, and those from protein increased if this is practicable. In most diabetic diets, therefore, the percentage of calories derived from carbohydrate should be approximately 40 per cent, from protein about 15 per cent and the remaining 45 per cent from fat.

The daily intake of *carbohydrate* to be prescribed ranges from the minimum sufficient to prevent ketonuria, that is, 100 g daily, to a maximum of 240-260 g. The upper limit is imposed by the fact that it is difficult to achieve satisfactory blood glucose levels throughout 24 hours with a daily carbohydrate intake greater than this. If the daily intake of carbohydrate is 240 g, approximately 50 g of carbohydrate will usually be provided by each of the three main meals, 20 g by each of three snacks and 30 g by one pint of milk (540 ml) taken in the course of the day. Experience has shown that it is very difficult to prevent an excessive rise in the blood glucose concentration after each meal with amounts larger than this. A simple method of calculating the carbohydrate content of the diet is to allocate a figure equivalent to one-tenth of the total calories to carbohydrate, that is, if a diet of 1,800 kcal is prescribed it should contain about 180 g of carbohydrate, providing 720 kcal or 40 per cent of the total.

The consumption of *protein* is largely determined by social and economic considerations and will frequently be lower than would be considered desirable. If this is the case, every effort should be made to increase the protein intake and to try to ensure that some protein is eaten at each main meal. An adequate consumption of protein is necessary in children and adolescents to ensure satisfactory growth, and since amino acids stimulate the beta cells of the pancreas to secrete insulin, in both normal subjects and in those with insulin-independent diabetes, a smaller rise in blood glucose concentration occurs when carbohydrate is consumed along with protein. In both categories of diabetic patients consumption of protein will also promote satiety and so help them to keep more strictly to their carbohydrate allowance. A minimum amount of protein should therefore be specified in all diabetic diets, but in the case of those who are not obese it should be emphasised that more than the amount specified may be taken if desired. The daily consumption of protein will usually lie in the range of 60-110 g.

The *fat* intake should be adjusted to bring the total calories to the level desired, and will usually amount to 50-150 g daily. Because diabetic patients have an increased risk of death from ischaemic heart disease, and because ischaemic heart disease may be related to the amount of saturated fat in the diet, the total amount of fat should be restricted even in those who are not obese. Plasma lipids, particularly cholesterol, should be checked regularly and if significantly elevated the diabetic diet may be appropriately modified on the lines of the diet on page 1000.

When the patient's requirements have been assessed the figures must be translated into practical and comprehensible instructions for the patient, using one of the types of diet prescription sheets described below.

Each patient should be given a cyclostyled or printed copy of the list of exchanges (p. 991) with instructions regarding the meals at which they may be taken. The diet sheet and exchanges must be discussed with the patient repeatedly and with a relative if necessary until the system is fully understood.

Types of Diet. Basically there are two types of diet: (1) measured, in which the amount of food to be eaten at each time of the day is specified, and (2) unmeasured, in which the patient is supplied with a list of foods grouped in three categories: foods with a high carbohydrate content which are to be avoided altogether; foods with a relatively low carbohydrate content which are to be eaten in moderation only; and non-carbohydrate foods which may be eaten as desired. An example is shown on page 996.

MEASURED DIETS. In these diets the portions of food may be measured either by weighing with scales or more simply by using household measures. Measured diets are required for two groups of patients, (*a*) those who require insulin or an oral hypoglycaemic agent, and (*b*) those who are overweight and require a strict reducing regimen.

Patients in group (*a*) should if at all possible weigh out the portions of food initially. They should be provided with a simple balance (available on NHS prescription) for this purpose. After a few weeks most patients are capable of assessing the weight of portions with sufficient accuracy by eye, and regular weighing becomes less necessary. However it is often valuable to check visual assessments by weighing from time to time. A method of constructing a sample diet of 1,800 kcal suitable for patients in group (*a*) is described on pages 990 to 993. The exchanges for carbohydrate, protein and fat on which it is based are set out on pages 991 to 993. It is important to realise that the exchanges or portions employed as units are arbitrary and are decided mainly in the light of the food habits of the population as a whole. The British Diabetic and Dietetic Associations have recommended that the carbohydrate unit should contain 10 g carbohydrate. In Britain the staple carbohydrate food is bread, and the basic carbohydrate exchange for the purposes of calculation is therefore taken to be $\frac{2}{3}$ oz bread which contains 10 g carbohydrate, along with 2 g protein and $\frac{2}{3}$ g fat. This is the reason why a carbohydrate exchange (p. 991) contains some protein and fat in addition to carbohydrate. Note also that a protein exchange contains some fat.

Diabetics who are obese should be urged to accept a reducing regime (p. 117). The method of achieving reduction in weight is the same for obese diabetic patients as for those with simple obesity. Diet No. 4 (p. 988) will meet the needs of many. The portions in this diet can be weighed out with scales but more usually are dispensed using household measures as described in this diet. It should be explained that such a strict diet is to be followed temporarily only until the standard weight is reached; thereafter the diet may be increased, and if the patient is sufficiently intelligent, advice can then be given on how to avoid monotony by using the list of exchanges for diabetic diets provided on pages 991 to 993.

UNMEASURED DIETS. If insulin or oral hypoglycaemic agents are not required and marked obesity is not present, it may not be necessary for the patient to follow such an accurate diet. Sometimes it may be impracticable to do so because of the patient's mental, visual or other physical incapacity or unwillingness to co-operate. Many patients develop the disease when they are already middle-aged or elderly and have a mild type of diabetes often associated with moderate obesity. For such patients an unmeasured diet of the type described on page 996 may be adequate.

ALCOHOL. Many diabetic patients need advice regarding the consumption of alcohol. There is no medical objection to taking alcoholic drinks in moderation provided the patient realises that he must take account of their calorie value and sometimes of their carbohydrate content. Beer for example may contain 10-30 g of carbohydrate per half litre (1 pint approx.) and with the alcohol this will provide 150-400 kcal, depending on the strength of the beer. Sweet wines and cider all have a high carbohydrate content, and spirits such as whisky and gin, while free of carbohydrates, contain about 70 kcal per 30 ml.

SWEETENING AGENTS. Advice may also be asked about sweetening agents and so-called diabetic foods and drinks. Saccharin has been employed as a sweetening agent for many years. It has no calorie value. Sorbitol, a glucose derivative, and fructose are also added to 'diabetic' foods and drinks for sweetening purposes. In moderate quantities neither will interfere with the action or requirements of insulin. If a patient is having difficulty in reducing weight or in maintaining a normal weight, then the use of substitutes for sugar should be discouraged, since they may perpetuate the patient's desire to eat sweet foods and thus make it more difficult for him to tolerate dietary restrictions. Diabetic chocolate has a high fat content and this must be taken into account.

Oral Hypoglycaemic Drugs

A number of compounds are effective in reducing hyperglycaemia in patients who would otherwise require insulin. The sulphonylurea compounds, tolbutamide and chlorpropamide, and to a lesser extent the biguanides, metformin and phenformin, have a place in the management of about 30 per cent of diabetic patients. Although their mechanism of action is different, the action of both groups depends upon a supply of endogenous insulin, and it is therefore futile and dangerous to attempt to control juvenile-onset diabetes with these compounds.

Sulphonylureas. *Tolbutamide* is the mildest, and probably also the safest, of the sulphonylureas. Since its effective action does not exceed six to eight hours it should be administered two to three times a day. The dose varies between 1 and 2 g daily. It is very well tolerated and toxic reactions such as skin rashes occur only rarely. Unfortunately, the relapse rate is relatively high.

Chlorpropamide has a biological half-life of about 36 hours, and an effective concentration can be maintained in the blood by a single dose at breakfast. The usual maintenance dose is between 100 and 375 mg daily; larger doses should not be used on a long-term basis, since above this level there is an increased risk of toxic effects, such as jaundice, drug rashes, and blood dyscrasia. Two other effects of clinical importance should be noted. If alcohol is taken following chlorpropamide an unpleasant flushing of the face occurs in some patients. Chlorpropamide may lead to severe hypoglycaemia, which can be very refractory to treatment. Great care must be taken to avoid this, particularly in elderly patients, and once glycosuria has been abolished and symptoms relieved, the daily dose of chlorpropamide must be reduced to the minimum required to maintain control. In fact many patients who require 375-500 mg daily initially can be maintained on a long-term basis on 100 mg or less per day.

Sulphonylureas are valuable in the treatment of patients with maturity-onset diabetes who fail to respond to simple dietary restriction and who are not overweight. Sulphonylureas should not be given to obese patients since they act by stimulating the production of endogenous insulin and this leads in turn to an increase in weight with a consequent reduction in life expectancy.

Biguanides. The biguanides are less widely used in Britain than the sulphonylureas, because of the higher incidence of side-effects, particularly gastrointestinal symptoms. However, the biguanides are valuable in two clinical situations. Firstly, since their administration is not associated with an increase in weight, they are to be preferred when it is essential to treat a patient with maturity-onset diabetes who is overweight but in whom hyperglycaemia persists despite efforts to adhere to a diet and reduce weight. Secondly, as the hypoglycaemic effect of the biguanides appears to be synergistic with that of the sulphonylureas, there is a place for combining the two when the sulphonylureas alone have proved inadequate (primary failure), and when, as happens with 5 to 10 per cent of patients, initial success is followed after several months or even one to two years by loss of control (secondary failure).

Metformin is less likely to cause gastrointestinal side-effects than *phenformin*, and is given with food in two or three daily doses of 0·5-1·0 g each. The usual dose of phenformin is 50-150 mg daily.

Clinical use of Sulphonylureas and Biguanides. Patients may be started on an oral hypoglycaemic drug as soon as it is clear that dietary measures alone are inadequate. It is usually possible to reach a decision on the success or failure of these drugs within a week, though occasionally a full response may not be apparent for considerably longer. Diabetics treated successfully in this way for prolonged periods may ultimately need an alteration of dose or a change of regime temporarily or permanently; in particular they may require insulin to meet the needs created by a severe infection, an operation or other stress.

Insulin

Unfortunately no method of giving insulin has yet been found that will maintain the blood glucose within the physiological range throughout the 24 hours without some risk of hypoglycaemia. However, with one or more of the preparations of insulin available it is usually possible to keep the blood glucose within reasonable limits throughout the day and night without undue risk of hypoglycaemia.

Two main forms of insulin are available, namely soluble and depot, and there are several varieties of depot preparations. These vary in the rate of onset and duration of their effect, as shown in Table 11.

All the therapeutic preparations of insulin are made in concentrations of 40 and 80 units per ml, and soluble insulin is also available in a concentration of 20 units per ml.

Soluble Insulin. This is a clear solution in contrast to the depot insulins which are cloudy. When injected subcutaneously, soluble insulin is rapidly effective (Table 11) but the action is relatively short-lived. A patient stabilised on soluble insulin alone would therefore need at least two injections in the day.

Soluble insulin is essential in the following circumstances:

(*a*) For new cases with severe dehydration or keto-acidosis.

(*b*) For emergencies associated with ketosis, such as acute infection, gastroenteritis and some surgical operations.

(*c*) For the treatment of nearly all young patients.

Depot Insulins. In a relatively small number of cases an adequate degree of control can be established by a single morning injection of depot insulin. Such patients are usually elderly with relatively mild diabetes. Most insulin-requiring diabetics however do best on a depot insulin with one or two supporting doses of soluble insulin. The choice of depot insulin in an individual case is determined by consideration of the patient's way of life, including his meal pattern, type of occupation, hours of work and recreation, in relation to the time of action of the various depot insulins. More insulin will be required to cover main meals and periods of inactivity, and vice versa.

Protamine Zinc Insulin (*PZI*). The addition of zinc and protamine to soluble insulin delays its release from the site of injection, so that PZI exerts its maximum effect on the blood glucose later, and the duration of action is longer, than soluble insulin (Table 11). Despite its prolonged action PZI does not always keep the blood glucose within acceptable limits throughout the 24 hours. Glycosuria is most likely to occur before the morning injection has taken full effect, and a dose of soluble insulin is generally required in the morning and sometimes in the evening, especially in young patients. Merely to increase the morning dose of PZI may result in severe hypoglycaemia later in the day or night. Indeed it is a good rule that the dose of PZI should not exceed 40 units at a single injection. When giving soluble insulin and PZI together, the two should not be mixed in the syringe, but may be given through the same skin puncture. If the two are mixed the excess of protamine in the PZI will convert some of the soluble insulin into PZI.

TABLE 11

Preparation of insulin	Hypoglycaemic effect	*Approximate* duration of effect in hours		
		Start	Maximum	Termination
Soluble	Rapid onset and short duration	½	4-6	6-10
Globin	Intermediate	2-3	6-10	10-14
IZS amorphous				
Isophane (NPH)				12-22
PZI	Slow onset and long duration	4-6	8-14	20-30
IZS crystalline				

Insulin Zinc Suspensions (*IZS*). The rate of release of these insulins from the tissues is related to the size of the insulin particles which are suspended in acetate buffer. Three preparations are available:

(*a*) IZS amorphous (*semilente*) insulin has a duration of action which is intermediate between that of soluble and protamine zinc insulin.

(*b*) IZS crystalline (*ultralente*) insulin is slower in action than IZS (amorphous) insulin (Table 11).

(*c*) IZS (*lente*) insulin is a mixture of three parts of amorphous with seven parts of crystalline material. This usually achieves uniform reduction of the blood glucose over 24 hours. It is dispensed when IZS is prescribed unless the prescription specifically orders semilente (amorphous) or ultralente (crystalline).

Globin Insulin. This is another depot insulin, intermediate in duration of action between soluble and protamine zinc insulin.

Isophane (NPH) Insulin. This is similar in action to globin insulin, though its effect is slightly more prolonged. Since isophane insulin contains an excess of soluble insulin it can be mixed in the same syringe as soluble insulin. This is convenient particularly if an automatic injector (for example a 'Hypogard' or a 'Palmer Injector') is used. Many younger patients are best treated with isophane and soluble insulin taken twice daily.

In practice one must be prepared to try combinations of the various insulin preparations, and to vary the time at which they are administered in the light of the results of urine tests and blood glucose estimations at different times of the day until smooth control is achieved over the 24-hour period. It is impossible to forecast the response of a patient to insulin, and the daily dose required to establish control varies from 10 to 100 units or more.

A practical point worth mentioning, since it may give rise to distress if not anticipated, is that blurring of vision (which may occur in a severe diabetic before treatment) may become noticeably worse after starting treatment with insulin. It is due to transitory osmotic abnormalities in the eye, especially the lens, and may persist for as long as several weeks after initiating treatment.

Choice of Therapeutic Regime

It must be emphasised that the regime eventually adopted in each case of diabetes is chosen by a process of trial, and that changes may be needed as more is learned about the patient and the kind of diabetes which he has.

The chief indications for the main types of therapeutic regimen are:

1. Practically all young patients who develop diabetes before the age of 40 require treatment with insulin. The majority will be best controlled by taking soluble insulin in the morning along with one of the depot insulins, most usually protamine zinc insulin or isophane insulin. In addition a second dose of soluble insulin, or of soluble and depot insulin (most commonly isophane insulin), may be required before the evening meal.

2. The majority of patients developing the disease over the age of 40 can and should be controlled by diet alone. This applies particularly to obese patients, but others who are not overweight may also do well on dietary therapy alone.

3. Those over the age of 40 who fail to achieve satisfactory control by dietary measures alone will usually respond well to a sulphonylurea if they are not obese, or to a biguanide if they are obese. If adequate control is not achieved by one drug, a combination of sulphonylurea and biguanide may be tried. If this fails insulin will be required.

4. Elderly patients who require insulin will often do well with a relatively small dose (20 units) of a depot insulin alone, such as PZI, IZS (lente) or isophane insulin. A few, particularly those who would otherwise require more than 40 units of PZI a day to be adequately controlled, should be given soluble insulin in addition.

It must be stressed again that obese patients should be treated by dietary restriction and weight reduction rather than by the administration of insulin or other hypoglycaemic agent. The advent of the 'insulin era' has obscured the remarkable improvement in glucose tolerance which usually results from reduction in weight. Insulin and the sulphonylureas increase the appetite, and thus may increase weight and intensify the total disability.

Initiation of Treatment

It is rarely necessary to admit diabetic patients to hospital for initial stabilisation. This statement applies both to patients who require treatment with insulin and those who do not. Indeed it is desirable that the patient learns to manage all aspects of his disorder as quickly as possible, and this can best be done as an outpatient while leading a relatively normal existence at home and at work. However, patients being stabilised on insulin have to be seen daily at first and if this is not otherwise possible, admission to hospital will be necessary. Hospital admission will also be necessary for patients with severe keto-acidosis.

As soon as the diagnosis is made a careful search is necessary to detect early evidence of the complications to which the diabetic is prone (p. 698). These include coronary artery disease and hypertension, obliterative arterial disease, peripheral neuropathy, cataract, retinopathy, nephropathy, pulmonary tuberculosis and other infections, particularly of the skin and urinary tract.

Patient's Education. 1. Every patient who is capable of learning must be taught how to test his urine with a Clinitest set (and sometimes with Acetest tablets also), to keep a record of the results in a notebook and to understand their significance.

2. All patients requiring insulin must learn to measure their dose of insulin accurately with an insulin syringe (B.S. 1619), to give their own injections and to adjust the dose themselves on the basis of urine tests and other factors such as illness, unusual exercise and insulin reactions. They should be made to experience an insulin reaction (p. 697) at a relatively early stage, so that they know what this involves, can recognise the early signs and take appropriate action.

3. All patients must have a working knowledge of diabetes, i.e. they must be able to recognise the symptoms associated with marked glycosuria and to understand their significance. They must be told that many drugs have undesirable effects on the diabetic state, as may also such other factors as illness of any kind or emotional upset. They should be advised to come to the doctor or the clinic at once, without prior appointment, as soon as they are aware of any deterioration in health or urine tests which does not respond rapidly to the simple measures that they take themselves.

4. All patients must know how to take care of their feet, and learn to treat any infected lesion with respect.

Education of the patient is time-consuming and repeated practical demonstrations may also be required. It may be supplemented by reading appropriate booklets. However, it is only in this way that diabetic patients can safely undertake all normal activities while maintaining good control of their disease. If the patient is a child, or is blind, mentally defective or otherwise incapable, instructions in these matters must be given to a parent, guardian or some other attendant.

It is a wise precaution for diabetic patients who are taking insulin or oral hypoglycaemic drugs to carry a card with them at all times stating their name and address, the fact that they are diabetic, the nature and dose of any insulin or other drugs they may be taking, and, in addition, giving the name, address and telephone number of their family doctor and any special diabetic clinic they may be attending. Suitable cards are provided by the British Diabetic Association for the use of members.

Supervision of Patient

Diabetics should be seen at regular intervals for the remainder of their lives. The object of these visits is to check the degree of control and if necessary to make appropriate alterations in treatment and to watch for any complications. Records should be kept so that the doctor is immediately on the alert if changes in health occur. The frequency of visits is determined by the severity of the disability, the reliability of the patient and his ability to manage his own condition.

For the general practitioner with diabetic patients scattered widely in his practice, this supervision may be difficult. For this reason and because of the need to develop and apply new and better techniques for the control of diabetes, many hospitals arrange diabetic clinics.

Assessment of Control

At the patient's regular visit to the diabetic clinic or to his general practitioner, the degree of control should be assessed by considering the patient's weight in relation to his standard weight; the results of urine tests; the blood glucose estimation; the presence or absence of symptoms of either hyper- or hypoglycaemia.

Urine Testing. Proper assessment of control is impossible unless in the course of his normal activity the patient tests samples of urine regularly. By selecting suitable times for the tests and tabulating the results, it is easy for the doctor or the experienced patient to decide whether the dose of insulin or hypoglycaemic drug should be increased or reduced, or whether the carbohydrate content of the diet or the time when it is taken should be altered.

Diabetics taking insulin should test samples of urine obtained before breakfast, before the mid-day and evening meals, and at bedtime (prior to a bedtime snack if this is taken). The patient must empty his bladder and discard this urine about 30 minutes before passing a specimen for testing. Otherwise the pre-meal specimen will include urine secreted into the bladder after the previous meal and will give the impression that the blood glucose concentration before meals is higher than it really is.

Patients treated by diet alone or with oral hypoglycaemic agents should test the first morning specimen and samples passed about two to four hours after

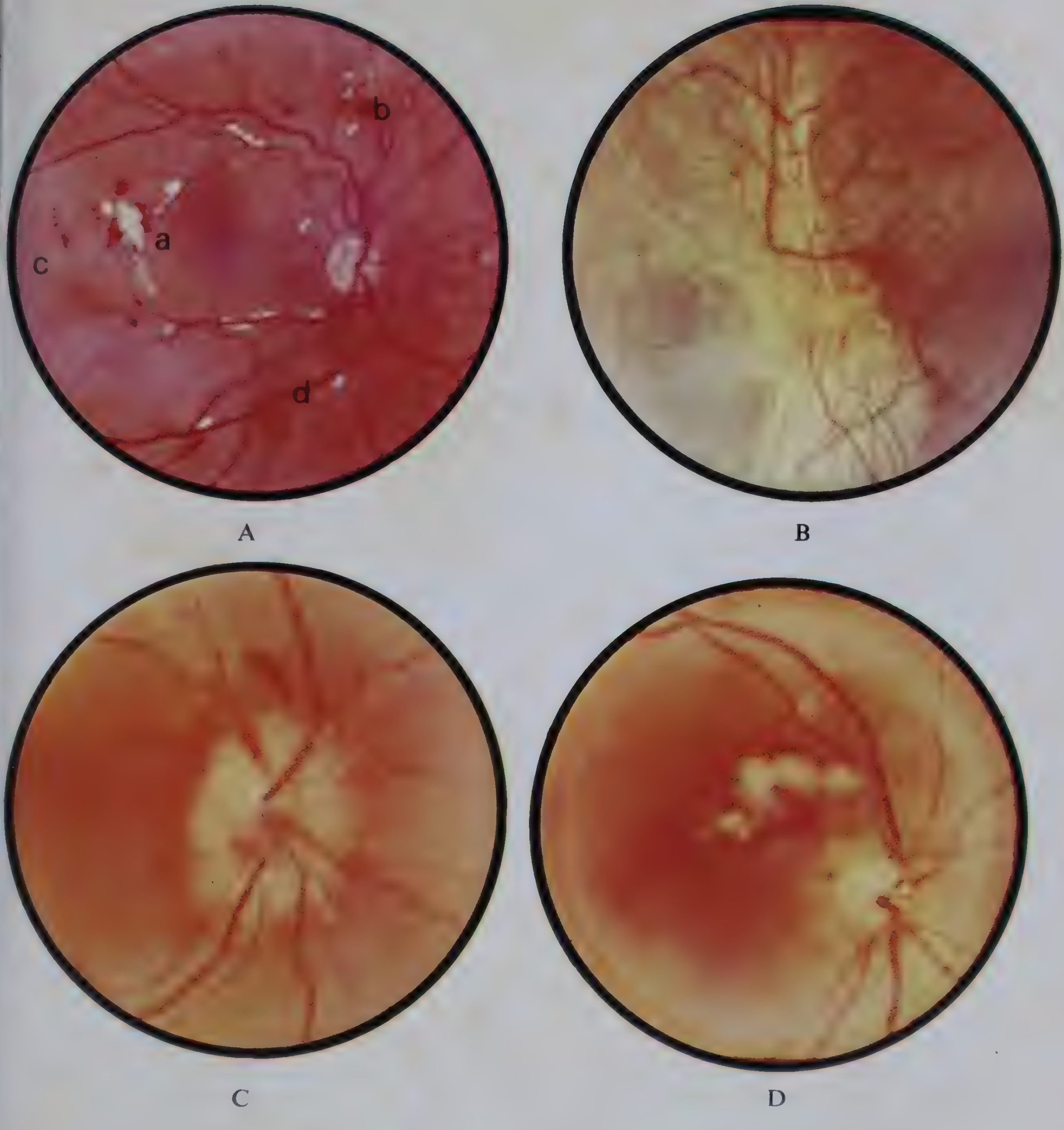


PLATE II

A, Diabetic retinopathy; (*a*) Exudates; (*b*) Dot haemorrhages; (*c*) Microaneurysms; (*d*) Congested veins. B, Advanced proliferative diabetic retinopathy. Heavily vascularised sheets of fibrous tissue are forming in the vitreous, mainly derived from the optic disc. C, Papilloedema. Note swelling of the disc and haemorrhages on or very near the disc. D, Thrombosis of the lower temporal branch of the central retinal artery. Note haemorrhages and exudates. There is also pathological cupping of the disc due to raised intra-ocular pressure which probably predisposes to retinal thrombosis.

(*By permission of Professor C. I. Phillips, Department of Ophthalmology, University of Edinburgh*)

the main meals of the day; the majority of such specimens should be either free of or contain ¼ per cent of glucose or less.

While the patient is being stabilised, tests will have to be carried out three or four times daily; when control is established the frequency can be greatly reduced. Three or four tests on a single day once or twice weekly are much more informative about the state of control than a single test carried out daily. A full series of tests should be undertaken therefore on one or more selected days each week.

Blood Glucose Estimations. At the patient's regular visits to the diabetic clinic, it is advisable to measure the blood sugar level as an additional index of the degree of control. In assessing the result it is important to consider the interval between taking the sample and the last meal and also previous physical activity. A series of estimations made over several months, or even years, provides a useful record of the patient's ability to control his disease. This is particularly important during pregnancy when the renal threshold may fall temporarily.

Insulin Reactions and Hypoglycaemia

If soluble insulin is administered to a normal person the blood glucose falls, producing symptoms that may begin to appear when the concentration is about 50 mg/100 ml and are fully developed at about 40 mg/100 ml. In diabetics who are constantly hyperglycaemic, the same symptoms may develop at much higher levels, e.g. 120 mg/100 ml or more.

In order of frequency the symptoms include a feeling of being weak and empty, hunger, sweating, palpitation, tremor, faintness, dizziness, headache, diplopia and mental confusion. Abnormal behaviour, leading occasionally to arrest by the police on a charge of being drunk and disorderly may also occur. Alternatively, and particularly in children, there may be lassitude and somnolence, muscular twitchings, deepening coma and convulsions.

Hypoglycaemia induces secretion of adrenaline, and this in turn causes tachycardia and tremor. Adrenaline, by mobilising liver glycogen, combats the hypoglycaemia. This homoeostatic reaction on the part of the body partly explains why patients rarely die of hypoglycaemic coma from too much soluble insulin. By contrast, coma is dangerous when it arises from a large dose of depot insulin or from an overdose of a sulphonylurea, particularly chlorpropamide. The latter condition although relatively uncommon is peculiarly resistant to treatment, since the drug reduces the hepatic release of glucose, and because the half-life of the drug is so long. The brain is dependent on the blood glucose for the energy necessary for its activity. For this reason, hypoglycaemia should be prevented from recurring by prompt reduction of the dose of insulin or of sulphonylurea.

Hypoglycaemia due to overdosage with soluble insulin comes on rapidly, at the time when the insulin is having its maximum effect (Table 11, p. 693), and usually passes off soon. Reactions from excessive IZS (lente) given before breakfast usually occur in the late afternoon and those from PZI at night or early next morning. These reactions begin gradually with little adrenaline response and become persistent and profound unless vigorously treated. The predominant symptoms are very variable and include headache, malaise, night sweats, nausea leading sometimes to troublesome vomiting, mental confusion and drowsiness, especially in the morning. Coma may follow.

Treatment of Hypoglycaemic Reactions. Since hypoglycaemia can easily be corrected if recognised early, it is useful for diabetic patients to experience the condition under supervision. In this way they learn to recognise the early symptoms. They must be made to realise that the most frequent causes of the condition are unpunctual meals and unaccustomed exercise, and seek to avoid both or to make adjustments to meet these circumstances. They should always carry some tablets of glucose or a few lumps of sugar for use in an emergency. Unless an attack of hypoglycaemia is adequately accounted for, the patient should reduce the next and subsequent doses of insulin by 20 per cent, and seek medical advice.

If the patient is so stuporous that he cannot swallow, he should be given an intravenous injection of 25 g of glucose (50 ml of a 50 per cent solution). This may have to be repeated. If this is not available, a subcutaneous injection of 0·5 ml of 1 in 1,000 solution of adrenaline may be tried, but it is relatively ineffective. Alternatively, the insulin-dependent patient may be given a subcutaneous or intramuscular injection of 1 mg of glucagon, repeated if necessary after 10 minutes. This raises the blood glucose by mobilising liver glycogen, and has the advantage of convenience in that it can be given by anybody capable of learning to use a syringe, but it may not be effective in severe and prolonged hypoglycaemia due to depot insulins. In addition to increasing hepatic glycogenolysis, glucagon stimulates the secretion of insulin and it should not be used to treat hypoglycaemia induced by an oral hypoglycaemic agent, since this may simply aggravate the disability by provoking further insulin secretion.

As soon as the patient is able to swallow, he should be given 30 g of sugar by mouth. Full recovery may not occur immediately, especially if the patient has been in coma for some time. Further, when hypoglycaemia has occurred in a diabetic using a depot preparation of insulin or a sulphonylurea, particularly chlorpropamide, the possibility of relapse within a day or more should be anticipated.

Repeated episodes of hypoglycaemia may lead to permanent intellectual deterioration; accordingly, adjustments to prevent recurrences are essential.

The Complications of Diabetes Mellitus

Diabetic Keto-acidosis

Prior to the discovery of insulin more than 50 per cent of diabetic patients ultimately died of keto-acidosis. Today this complication is preventable and accounts for less than 2 per cent of diabetic deaths. However, both the incidence and the mortality rate are still regrettably high. Failure of the patient to understand his disease, and failure to appreciate the significance of symptoms of poor control are the most common causes. Thus its prevention is largely a problem of education of patients and at times of their physicians. A clear understanding of the biochemical disorders involved (p. 677) is essential for its efficient treatment which should aim at having the patient out of danger within 24 hours.

Water and Mineral Depletion. The deficit of total body water in a severe case may be about 6 litres. About half of this is derived from the intracellular compartment and occurs comparatively early in the development of acidosis with relatively few clinical features; the remainder represents loss of extracellular fluid sustained largely in the later stages. It is at this time that marked contraction of the size of the extracellular space occurs, with haemoconcentration, a decrease in plasma volume, and finally a fall in blood pressure with associated renal ischaemia and oliguria.

The concentration of sodium and potassium in the serum gives very little indication of total body losses, and may even be raised due to disproportionate losses of water. Sodium loss, mainly from the extracellular space, may amount to as much as 500 mEq. Potassium loss from the cell may be 400 mEq or more. The concentration of potassium in the plasma in these circumstances is dependent on the balance between catabolism of protein and glycogen and haemoconcentration on the one hand, and urinary excretion on the other. Since the former generally exceeds the latter a high level of plasma potassium is likely to be present initially, in spite of a total body deficit. However, within a few hours of beginning treatment with insulin, there is likely to be a precipitous fall in the plasma concentration of potassium. At least three mechanisms are responsible for this: dilution of extracellular potassium by the administration of potassium-free fluids, the movement of potassium into the cells as the result of insulin therapy, and the continuing renal loss of potassium.

Keto-acidosis. The mechanism of the development of this state has been described on page 678. Apart from the clinical findings, the severity of the condition can be rapidly assessed by measuring the plasma bicarbonate, a level of less than 12 mEq/*l* indicating severe acidosis. The blood pH is an even more valuable guide but its measurement may not be so readily available. There are no simple and accurate quantitative methods for the determination of plasma ketones.

Clinical Features. Any form of stress, particularly an acute infection, can precipitate severe keto-acidosis in even the mildest diabetic. The most common cause is neglect of treatment due to carelessness, misunderstanding or illness, and failure to adjust the therapeutic regimen in the event of an acute infection.

The *symptoms* of diabetic keto-acidosis invariably include intense thirst and polyuria. Constipation, muscle cramps and altered vision are common. Sometimes, especially in children, there is abdominal pain, with or without vomiting. Hence diabetic keto-acidosis is important in the differential diagnosis of the acute abdomen. Weakness and drowsiness are commonly present, but it should be remembered that the state of consciousness is very variable and a patient with dangerous ketosis requiring urgent treatment may walk into hospital. For this reason the term diabetic keto-acidosis is to be preferred to the traditional 'diabetic coma', which suggests that there is no urgency until unconsciousness occurs. In fact it is imperative that energetic treatment is started at the earliest possible stage.

The *signs* include a dry tongue and soft eyeballs due to dehydration: 'air hunger' indicated by long, deep, sighing respirations; a rapid, weak pulse, and

deep inspiration followed by
slow audiable expiration

low blood pressure; sometimes abdominal rigidity and tenderness; the smell of acetone in the breath; ultimately coma supervenes.

Laboratory tests show (1) ketonuria and severe glycosuria; (2) blood glucose usually between 400 and 800 mg/100 ml, but it may be much higher and in some cases lower; (3) low plasma bicarbonate and blood pH; (4) normal or raised serum sodium and potassium; (5) leucocytosis.

It should be noted that the degree of hyperglycaemia and keto-acidosis do not always necessarily correlate well. Even at a level of blood glucose as low as 350 mg/100 ml, life-threatening acidosis may be present; on the other hand diabetic coma can occur, usually in elderly patients, with extreme hyperglycaemia and dehydration but no keto-acidosis, so called *hyperosmolar diabetic coma.*

Treatment. This condition should be treated with the utmost urgency in hospital. Intravenous therapy is required since even when the patient is able to swallow, fluids given by mouth may be poorly absorbed. Establishing an intravenous infusion can be technically difficult because of collapsed veins, but cutting down and tying in a cannula should be avoided if at all possible, because the veins may be needed again. Treatment must be checked against the blood concentration of glucose, potassium and bicarbonate estimated at intervals of not longer than two hours. Only in this way can the metabolic disorder be corrected accurately and rapidly. The aim should be to overcome with all speed:

1. Ketosis, by means of insulin to permit glucose utilisation.
2. Peripheral circulatory failure, acidosis, and water and electrolyte depletion, by means of appropriate intravenous fluids.
3. Infection, if present, by means of antibiotics.

Figure 88 (p. 701), shows an example of a moderately severe case of diabetic ketosis treated on these lines.

Ketosis and dehydration render the comatose patient very resistant to insulin. Only soluble insulin should be used and 100 units should be given immediately the diagnosis is made, half intravenously and half intramuscularly. The total amount of insulin required varies widely and must be assessed in the light of changes in the blood glucose level; severe cases will usually need at least 500 units in the first 24 hours and may require considerably more. As long as there is evidence of peripheral circulatory failure some of the insulin should be given intravenously.

The deficit of extracellular fluid, which is likely to be about 3 litres, should be made good by infusion of saline isotonic with plasma (0·9 % NaCl). In cases which are also severely acidotic (bicarbonate < 12 mEq/*l*), ½ litre of the isotonic saline may be replaced by isotonic sodium bicarbonate (1·3 %) or, if this is not available, by isotonic sodium lactate solution (M/6). The intracellular deficit of water, usually about 2-3 litres, must be replaced by giving 5 per cent glucose and not by more saline. It is best given when the blood glucose is approaching normal. It is important to continue the intravenous glucose together with appropriate doses of soluble insulin subcutaneously until the ketonuria has disappeared and the water deficit has been made good.

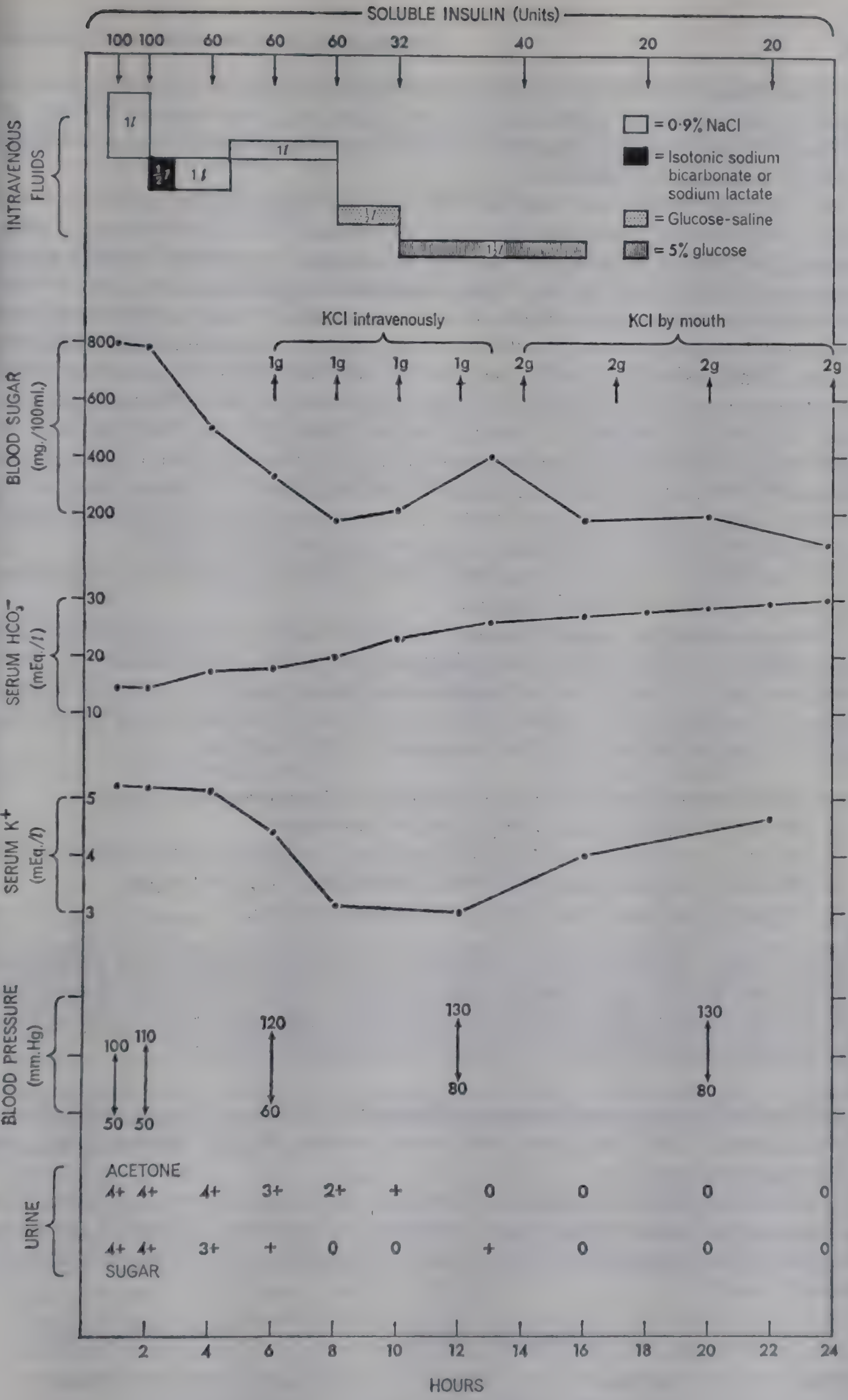


FIG. 88

Chemical pathology and response to treatment of a moderately severe case of diabetic keto-acidosis during the first 24 hours in hospital.

If the patient is admitted in profound circulatory failure, or the blood pressure remains low after the administration of saline and bicarbonate, it may be necessary to give blood or plasma. Vasopressor drugs as used for the treatment of shock may also be required.

Every patient in diabetic keto-acidosis is potassium depleted and many will require intravenous potassium (p. 191) to prevent the development of dangerously low levels of potassium during the course of treatment. As the serum potassium is often high at the time of diagnosis it is important not to start potassium therapy until the level in the serum has fallen to normal, the peripheral circulation has been restored, and the urinary output is adequate. Approximately 80 mEq of potassium may safely be given by vein in the first 16 hours but much more than this may be required. It is important to realise that sufficient potassium must be given to maintain a normal serum concentration, and this can be confirmed only by frequent estimations. It is customary to add 1 g potassium chloride (13·4 mEq potassium) to each 500 ml of glucose and water given intravenously. Once oral feeding has started 2 g potassium chloride should be given four-hourly for two to three days to restore the total body deficit.

In a stuporous or comatose patient, gastric aspiration should be undertaken to avoid the risk of inhaling vomitus.

Infections must be carefully sought and vigorously treated since it may not be possible to abolish ketosis until they are controlled. Once ketosis has been overcome, and the water and salt deficit made good (usually in about 24 hours), feeding by mouth can be started with frequent small fluid feeds each containing about 25 g of carbohydrate. Five examples of such feeds are:

1. 100 ml (3½ oz) fruit juice plus 15 g (½ oz) of cane sugar or glucose.
2. 200 ml (7 oz) milk plus 180 g (6 oz) of porridge.
3. 200 ml (7 oz) milk plus 20 g (⅔ oz) Ovaltine, Horlicks or similar preparation.
4. 200 ml (7 oz) milk plus 10 g (⅓ oz) cereal plus 7 g (¼ oz) sugar.
5. 200 ml (7 oz) milk plus 20 g (⅔ oz) Benger's Food.

Enough insulin should be given to prevent any further ketonuria or glycosuria. Control can be lost very quickly; frequent blood sugar estimations are needed and soluble insulin should be given before each oral feed, even if the urine is free of sugar and only very small doses of insulin are required.

Differential Diagnosis of Coma in a Diabetic. Confusion between coma due to hypoglycaemia and that associated with ketosis should seldom arise; the distinction is clear.

It should be noted that diabetic coma may occasionally pass undetected into hypoglycaemic coma through too enthusiastic treatment; likewise, vomiting induced by hypoglycaemia from a depot insulin may continue until diabetic coma develops.

	Hypoglycaemic Coma	*Coma with Ketosis*
History:	no food	too little or no insulin
	too much insulin	an infection
	unaccustomed exercise	digestive disturbance

	Hypoglycaemic Coma	*Coma with Ketosis*
Onset:	in good health immediately before related to time of last injection of insulin	ill-health for several days before
Symptoms:	of hypoglycaemia; occasional vomiting from depot insulins	of glycosuria and dehydration; abdominal pain and vomiting
Signs:	moist skin and tongue	dry skin and tongue
	full pulse	weak pulse
	normal or raised blood pressure	low blood pressure
		reduced intra-ocular tension
	shallow or normal breathing	laboured breathing ('air hunger')
	brisk reflexes	diminished reflexes
	plantar responses usually extensor	plantar responses usually flexor
Urine:	no ketonuria	ketonuria
	no glycosuria, provided that the bladder has been recently emptied	glycosuria
Blood:	hypoglycaemia	hyperglycaemia
	normal plasma bicarbonate	reduced plasma bicarbonate

Vascular Disorders

Vascular disease, arterial, arteriolar and capillary, is the largest and most intractable problem in clinical diabetes. Arterial disease is easily the commonest cause of death in diabetics over the age of 50, and the mortality rate is far higher than expected, while nephropathy accounts for more than half the deaths under 50. Moreover, diabetes is the most important systemic disease causing blindness. Strict control probably offers the best chance of delaying the onset and progress of the vascular complications of diabetes. Unfortunately, however, they may develop despite every effort by both patient and doctor to maintain precise control of the diabetic state.

Atherosclerosis occurs commonly and extensively in diabetics. The pathological changes in diabetics are not specific in a qualitative sense but they occur earlier and are more widespread than in non-diabetics. Thus diabetics are more prone at an earlier age than other people to intermittent claudication, gangrene of the toes and feet and myocardial infarction.

From the clinical viewpoint the peripheral pulses in the legs are often diminished or impalpable, and particularly in elderly patients, ischaemic changes in the feet are frequently apparent. Defective circulation in the legs resulting in poorly nourished tissues predisposes to the dangerous complication of gangrene. If a painless peripheral neuropathy (p. 706) is present, this may also be of aetiological importance, since the patient will tend to ignore or neglect injuries and other damage to the tissues. Diabetic gangrene usually starts in one foot, following a trivial injury—the cutting of a corn, or a burn from a hot water bottle. Toxic absorption from necrotic tissue and secondary infection may kill the patient unless the limb is amputated. Amputation of a toe, a foot, or even a whole leg is sometimes necessary to save life.

A great deal can be done to prevent this serious complication by instructing diabetics with a poor circulation to wear properly fitting shoes, to use bed-socks rather than hot water bottles, never to cut their own corns and to 'keep their feet as clean as their face'. The services of a skilled chiropodist are invaluable.

Diabetic Nephropathy. A specific type of renal lesion may occur as a result of the changes in the basement membrane of the glomerular capillaries. This is known as *diabetic glomerulosclerosis*, and there are two types, diffuse and nodular: the former is the more common and consists of a generalised thickening of glomerular capillary walls. The nodular type is a development of this, and in these cases rounded masses of acellular, hyaline material are superimposed upon the diffuse lesion in the glomeruli. These nodules are sometimes called Kimmelstiel-Wilson bodies. Diabetic glomerulosclerosis can be seen by light microscopy in about 70 per cent of diabetic patients at autopsy. In the early stages of diabetes there may be little or no clinical evidence of renal involvement, and even with well-established diabetic glomerulosclerosis the patient may exhibit only slight to moderate proteinuria. In some cases, however, the patient develops marked proteinuria and the nephrotic syndrome with increasing renal failure and uraemia.

There is no way of preventing or modifying the progression of nephropathy once this is clinically apparent as proteinuria. In the later stages the management is the same as in other forms of chronic renal disease (p. 599).

Diabetic Retinopathy. The ophthalmoscopic findings may be sufficiently specific to enable the physician to make the initial diagnosis of diabetes (Plate II, p. 696). Features of diabetic retinopathy include: micro-aneurysms of the capillaries; irregularity and tortuosity of the veins; haemorrhages, usually round; hard exudates; new vessel formation; fibrous proliferation, occurring mainly in association with neovascularisation; and vitreous detachment. They are seen in varying combinations in different patients.

Micro-aneurysms, abnormalities of the veins, and new vessels do not of themselves interfere seriously with vision, but the other elements of retinopathy may do so. Retinal or pre-retinal haemorrhages will seriously affect vision if they involve the macula, or if they break through into the vitreous, when sudden severe visual loss is usual. Exudates are also associated with symptoms if the macula is involved. Unfortunately all these lesions occur most frequently within 4 to 5 disc diameters from the disc; the region just temporal to the macula being often first involved. New vessels appear most commonly at the disc, but can originate anywhere except at the macula. The new vessels in themselves do little harm, but they leak serous fluid which causes vitreal-retinal adhesions followed by vitreous contraction. The latter puts traction on the friable new vessels so that vitreous haemorrhage and retinal detachment may occur and cause blindness.

From the clinical point of view, patients with only micro-aneurysms, retinal haemorrhages and exudates are classified as having *simple retinopathy*; while those with pre-retinal haemorrhages, new vessel formation or fibrous proliferation are classified as having *malignant retinopathy*.

As with nephropathy, duration of diabetes is the most important factor influencing the occurrence of retinopathy, the course of which is very variable. However in general, prognosis for vision is good for patients with simple retinopathy, especially if they are young, and bad for those with malignant retinopathy, of whom half are blind within five years. This fact has led to numerous types of proposed treatment, including pituitary ablation and photocoagulation of new retinal vessels. The variable nature of the natural course makes assessment of the effectiveness of any treatment extremely difficult, and the value of all those proposed so far remains uncertain, particularly in relation to the preservation of useful vision.

Cataract

Very rarely a specific type of opacity of the lens (cataract) occurs in diabetic children whose disease has not been adequately controlled. Cataract also occurs in elderly diabetics, but is said to be no more common than in other elderly people.

Infections

Lowered resistance to infection is associated with poor control of diabetes. The following forms are especially important.

Carbuncle. The development of a carbuncle may unmask latent diabetes; it may even precipitate ketosis and coma. The diabetic state brought on by a carbuncle is not invariably permanent; glucose tolerance may return to normal (at least temporarily) when the infection subsides. Cleanliness is a special virtue in the prevention of skin infection in diabetes. Once infection has occurred a suitable antibiotic must be used.

Pulmonary Tuberculosis. If a diabetic under treatment shows unexplained loss of weight, increase in insulin requirements or symptoms of pulmonary disease, clinical and radiological examination of the lungs should be undertaken. Pulmonary tuberculosis can be arrested in its early stages by prompt recognition and specific treatment, and every newly diagnosed diabetic should have a radiological examination of his chest.

Urinary Tract Infections. The presence of glucose in the urine provides a favourable medium for the growth of bacteria. Intractable infections of the urinary tract frequently occur, and for this reason catheterisation in particular should be avoided. Once infection has occurred treatment consists in controlling the glycosuria and the administration of suitable antibiotics as for any other case of urinary tract infection (p. 606).

Vulvitis. Pruritus vulvae is very commonly associated with moniliasis in the diabetic woman. *Candida albicans* is nearly always present. In the majority, the treatment is abolition of glycosuria which brings rapid relief. In a few cases local treatment with nystatin cream and pessaries may be required.

Diabetic Neuropathy

Peripheral neuropathy is a frequent complication of diabetes at any stage, which in the majority of cases may be unnoticed by the patient, but in some may give rise to troublesome symptoms. Motor, sensory or autonomic nerves may be involved, usually in a symmetrical manner.

1. *Chronic peripheral neuropathy* is the most common form of this disability. It occurs only rarely in diabetics under 20 years of age, but is frequent in elderly diabetics with long-standing disease. Since it also occurs in elderly people who do not have diabetes, degenerative disease of the vasa nervorum is thought to contribute to its development. In most cases symptoms are slight or absent; in others there may be pain, muscle tenderness and paraesthesiae in the limbs. The pain is characteristically confined to a leg or foot, its distribution is commonly in the anterior femoral region and it tends to be worse in bed at night.

The findings are confined to the lower limbs. Absent or diminished tendon reflexes are characteristic, the ankle jerks being mainly affected. Diminution or loss of vibration sense at the ankle or knee is also common. In advanced cases loss of other forms of sensation may be detected. Trophic changes may appear on the feet and ankles in severe chronic neuropathy; ulceration may develop secondarily to trivial trauma and disorganisation of joints may occur, resembling the Charcot joints seen in tabes dorsalis.

This type of neuropathy bears little relation to the quality of control and is unresponsive to treatment.

2. *Involvement of the autonomic nervous system* may cause diarrhoea, overflow incontinence of urine, impotence, postural hypotension and disturbances of sweating and skin temperature regulation. Involvement of the autonomic nervous system may result in an impaired sympathetic response to hypoglycaemia so that the patient no longer experiences the classical warning symptoms.

Like chronic peripheral neuropathy, autonomic neuropathy seems to bear little relation to the degree of control and to be unresponsive to treatment.

3. *Acute peripheral neuropathy* merges clinically with group 1, but is distinguished by its association with poor control, and by its improvement with adequate control of the diabetes, and by the fact that pain and paraesthesiae are usually more severe.

4. *Diabetic amyotrophy* is a predominantly motor form of acute diabetic neuropathy. It consists of bilateral symmetrical wasting and weakness of the pelvic girdle musculature with concomitant pain. With good control of diabetes, recovery is the rule after months or even years.

Special Problems in the Management of Diabetes

Diabetes in Children

Fortunately diabetes is not common in childhood, but when it occurs it is relatively severe and always requires treatment with insulin. The therapeutic problem of matching the dose of insulin to the food intake raises practical difficulties.

Food. The nutritional needs of diabetic children are essentially no different from those of other children. Since they should be growing, their caloric requirements are large in proportion to their size, by comparison with adult standards. Difficulties may be experienced in finding the best means of providing the requisite calories. In children, likes and dislikes for particular foods are often fickle and unpredictable. It is important to make sure that the child does not become too fat; hypoglycaemia due to too much insulin can lead to excessive appetite and hence to obesity. A dietitian can do much to help the child and his parents. A diabetic child must not have sugar or sweets, but the essential composition of his diet need differ little from that of his friends. It is important that everything possible should be done to avoid distinguishing him from his contemporaries. Once properly trained, he may go with them to a summer holiday camp if he so desires, provided that the camp organiser understands his disease. The British Diabetic Association runs special camps for diabetic children.

Insulin. Day-to-day requirements for insulin are often very variable. Children must not be expected to lead the steady life of a business man or housewife; their emotions and activities fluctuate unexpectedly—sometimes wildly active and sometimes sulking. This may have an important effect on their daily needs for insulin; excessive activity may result in hypoglycaemia, whilst lethargy may lead to hyperglycaemia. The latter may also be caused by any one of the numerous infectious diseases to which all children are prone. A combination of one of the depot insulins and soluble insulin before breakfast and usually a second dose of soluble insulin and if necessary a depot preparation before supper is a suitable arrangement for most diabetic children.

Diabetes in Pregnancy

One of the important consequences of the discovery and use of insulin is that diabetic women can now have children, whereas in the pre-insulin era they were almost always amenorrhoeic and infertile. If a diabetic woman wishes to have a child there is no reason why she should avoid pregnancy, provided that she suffers from none of the more serious complications of diabetes and provided she remains constantly under expert medical care.

Nevertheless pregnancy in a diabetic woman carries certain definite risks; in the later stages of pregnancy she may develop an excessive accumulation of amniotic fluid (hydramnios); in addition the fetus is sometimes unusually large leading to difficulty in labour. Moreover the chances that a diabetic mother may lose her baby either from a stillbirth or in the early neonatal period are greater than those of a non-diabetic mother, even with the most careful supervision.

The proper treatment of a pregnant diabetic patient requires the close and co-ordinated supervision of a team consisting of physician, obstetrician, anaesthetist, nurse and dietitian. The sooner the pregnancy is diagnosed the better. Some non-pregnant diabetic women often miss one or more menstrual periods, especially if their disease is poorly controlled. For this reason a laboratory test for pregnancy is often helpful. There are grounds for suggesting that oral hypoglycaemic agents might be teratogenic, and any diabetic patient who is taking these drugs and becomes pregnant should change to a preparation of insulin as soon as the pregnancy is diagnosed.

It is desirable that the expectant mother should spend a week as an ambulant in-patient in hospital towards the end of the third month of pregnancy. This will enable the patient and the team to get to know each other. Every effort must be made at this time to see that her diabetes is under the best possible control; further education of the patient may be needed in the proper management of her diet and insulin while at home. The diet, at first at least, need differ in no important respect from the diabetic diet (Diet No. 5, p. 995) to which she has been accustomed, but may need adjustment later, particularly with additional milk. Practical problems may be created for the physician and dietitian by bouts of vomiting that commonly occur in the early stages of any pregnancy, and by the peculiar food fads which many pregnant women develop.

After the diagnosis of pregnancy has been made the patient should be seen at first at fortnightly and later at weekly intervals. Continued full control of the diabetes may be complicated by other factors. First, the renal threshold for glucose often falls as pregnancy advances. This is a normal phenomenon, but in the diabetic it means that the tests for glycosuria which she carries out at home may cease to be a reliable index of diabetic control. Further, in the later stages of pregnancy lactosuria may occasionally occur and may lead to confusion. If excessive amounts of glucose are lost in the urine because of the lowered renal threshold, it may be necessary to give additional carbohydrate feeds between meals and sometimes at night, covered by suitable amounts of soluble insulin to avoid ketosis. Then, too, the requirements for insulin usually increase as pregnancy advances. Frequent estimations of blood glucose are needed to ensure that an increase in insulin dosage, based on misleading urine tests, is not producing hypoglycaemia; or alternatively, that hyperglycaemia is not insidiously building up through failure to give enough insulin to meet an increase in insulin requirements.

Pregnancy in a diabetic woman should seldom if ever be allowed to proceed to term. The chances of survival for the infant are greatly enhanced if it is delivered between the thirty-sixth and thirty-eighth weeks by induction of labour or if necessary by Caesarean section. Following delivery the insulin requirements of the mother fall considerably. Frequent blood glucose estimations and co-operation between the physician and dietitian are needed to ensure an uneventful return to the former diet and insulin dosage.

A final word of warning is necessary. It has already been indicated that sugar in the urine is not unusual during normal pregnancy, either because of a fall in the renal threshold for glucose or through lactose appearing in the urine. The finding, however, of reducing substances in the urine of a pregnant woman should never be lightly dismissed as a normal phenomenon. Full clinical investigation to exclude diabetes is essential; otherwise a preventable catastrophe may follow.

Diabetes and Surgery

Any surgical operation, however minor, and the accompanying anaesthetic cause a metabolic stress which the diabetic is less well able to meet than the normal person. The stress is temporary and will not be aggravated by a mild hyperglycaemia, but an accompanying acidosis will prejudice normal recovery. The position is worse if there is tissue wasting with much breakdown of fat and protein and the excretion of large amounts of potassium, phosphate and other intracellular electrolytes.

Two points must be kept in mind: first, the need to provide an adequate supply of energy for the tissues, and secondly, the need to be constantly on the alert for acidosis.

In practice there are two separate problems. The first is the management of a stabilised diabetic who has to undergo an operation at a time which can be chosen by the surgeon and physician. The second is that of a diabetic whose disease may not be well controlled and who suddenly has to be operated upon because of trauma, acute sepsis or a major abdominal or other catastrophe, or one who is first discovered to be diabetic immediately before operation.

As both the severity of the diabetes and the extent of the operation will vary greatly, it is not possible to set out details of management. Each patient is an individual problem.

Elective Surgery in a Stabilised Diabetic. All diabetics must be admitted to hospital about three days before an operation, even a minor one. During this period the control of the diabetes can be checked thoroughly. Provided a diabetic goes to the theatre in good condition, there is unlikely to be any significant change in the blood glucose, plasma bicarbonate or ketone levels during the time he is undergoing surgery. In fact, hypoglycaemia is more likely to occur than acidosis. For this reason it is generally advisable to give no insulin immediately before operation. During the day preceding the operation the patient's usual diet and doses of insulin should be given though doses of depot insulin of more than 20 units should be reduced by half and a supplementary dose of soluble insulin given later that day instead. It will usually be possible to arrange for the operation to take place in the morning. The patient should receive no breakfast and nothing by mouth before operation. Before being transferred to the theatre the fasting blood glucose level should be determined. If this lies between 120 and 200 mg/100 ml then no glucose or insulin need be given. If the level is below 120 then about 25-40 g of glucose should be given intravenously, preferably in hypertonic solution, in order to prevent possible hypoglycaemia during the operation. No insulin is necessary. If the fasting blood sugar is over 200, which is infrequent, then some insulin will be required. About one-third of his usual total daily dose is indicated, in the form of soluble insulin, but its administration can usually be postponed until after operation.

Recovery from the anaesthetic must be carefully supervised. The sooner the patient returns to his usual diet the better. This interval may be a few hours or several days, depending on the nature and severity of the operation. Within a few hours of recovery from the anaesthetic many patients are able to take a fluid or semi-fluid feed containing 25 g of carbohydrate (p. 702) at three- to four-hourly intervals, covered by suitable doses of soluble insulin. Some insulin-dependent diabetics after a major operation may need to have most of their energy requirements supplied as glucose, either intravenously or by mouth. If all has gone well, a single determination of the fasting blood glucose each morning will suffice. If recovery is stormy, measurements may be necessary at four-hourly intervals or even more frequently. Determination of the plasma bicarbonate or CO_2 combining power and electrolytes in the blood will also be helpful. The insulin dosage will depend on these findings, and until stability has been regained only soluble insulin should be used.

Each specimen of urine must be tested for sugar and ketone bodies. If ketosis develops it is essential to take immediate steps to increase the metabolism of glucose by adjusting the dose of insulin.

Diabetes and Surgical Emergencies. Circumstances vary so much that it is impossible to consider them except in the most general way. The essentials are to maintain the oxidation of glucose by the tissues at a sufficient rate and to combat acidosis and electrolyte disturbances when they occur. This can be done effectively only if the state of the diabetic control is assessed continuously and accurately. A laboratory service that can provide rapid results is thus essential. As long as the surgical condition remains untreated and the 'metabolic stress' continues, the diabetic condition is likely to get worse. Once the patient's surgical condition is under control he may be expected to respond promptly to the appropriate therapy for his diabetes.

Prognosis of Diabetes

The prognosis in diabetes has improved steadily since the introduction of insulin; but even with its use the average expectation of life is still rather less than that of a non-diabetic. It may be difficult to estimate the prognosis of an individual patient because so many variable factors have to be considered. Thus the child of parents poor in means and education, who is first seen in coma, obviously has a very different future compared with the middle-aged lady in easy circumstances who complains of nothing but a little thirst and pruritus, and can afford the time and the means to follow precisely the diet prescribed for her. The incidence of the complications of diabetes is mainly related to the duration of the disease but probably also to the precision with which it has been controlled.

Prevention of Diabetes

Diabetes is a disease of the prosperous, and in wealthy countries it is one of the major health problems. The hardships of the Second World War were associated with a marked decline in the incidence of diabetes in European countries; rationing of both food and petrol was probably responsible. The importance to health of sufficient exercise and of avoiding dietary excess has been stated repeatedly. Diabetes, like obesity and atherosclerosis, is likely to arise in predisposed persons who eat too much and exercise too little. Excess of dietary carbohydrate may strain the limited capacity of the pancreas to produce insulin, especially if it is in the form of sugar or other refined carbohydrate; excess of dietary fat may accelerate the complications of diabetes; atherosclerosis is a common cause of death in diabetics. In any event the public should be warned primarily against an overall excess of calories.

Screening. It is much easier to control the disease and to maintain the health of the patient in a state which allows him to lead a normal life, if the diagnosis is made early in the course of the disease. In many patients, the biochemical changes can be detected before the symptoms are sufficiently severe to make them seek medical advice. Any screening technique is expensive and should only be used if it is likely that a significant number of new diabetics will be recognised. High-risk groups, for example the first degree relatives of known diabetics, the obese and the mothers of babies weighing more than 10 lb at birth, will give a particularly high yield. The prevalence of diabetes in different communities varies from 0·5 to 5 per cent. About half of the cases may be unaware that they have the disease. These figures vary widely according to the social and economic state of the people and the educational and medical services available.

Urine testing has been widely used as a screening procedure. As up to 3 per cent of people may have renal glycosuria and so will have to be recalled for blood tests, and as a number of undoubted diabetics will be missed owing to their raised renal threshold for glucose, this is an unsatisfactory procedure. Whenever practicable, estimation of the blood glucose two hours after 50 g glucose orally is recommended as the screening procedure. Auto-analysers enable large numbers of samples to be tested daily.

Quite apart from screening high-risk groups it is not difficult to make out a case for a routine test of the urine for glucose in every full clinical examination; and all those with glycosuria (albeit of minor degree) should be considered diabetic until proved otherwise.

Genetic Counselling. Diabetic patients will often consult their doctor about the advisability of having children and sometimes it is his duty to warn them of the dangers. They can be told that the risks of pregnancy and delivery are little greater for a diabetic mother than for a normal woman, provided she submits to the strict discipline required (p. 707). The chances that she will produce a healthy baby are also good, but not quite so good as for a normal mother. The chances that her child will subsequently develop diabetes are higher than normal. If both parents have diabetes, the probability is that about 25 per cent of their children will develop the disease at some stage in life. The risk is about half this if only one parent is affected. Many diabetics have healthy children, and how strongly a doctor should word these necessary warnings is a matter for judgement in each case. The family history, the severity of the disease in the parents and their educational and economic background, must all be considered.

Conclusion. The management of a patient with diabetes mellitus offers a special opportunity for good medical practice, there being few other chronic diseases in which efficient management makes so much difference to the patient's life. The problems presented by the aetiology of diabetes and its long-term complications continue to offer some of the most demanding and fascinating challenges in medical research today.

JOYCE D. BAIRD.
J. A. STRONG.

Books recommended:

Bondy, P. K. (1969). *Duncan's Diseases of Metabolism*, 6th ed. London: Saunders.
Oakley, W. G., Pyke, D. A. & Taylor, K. W. (1968). *Clinical Diabetes and its Biochemical Basis*. Oxford: Blackwell.
Passmore, R. & Robson, J. S. (1973). *Companion to Medical Studies*, Vol. 3. Oxford: Blackwell.
Williams, R. H. (1968). *Textbook of Endocrinology*, 4th ed. London: Saunders.

Diseases of the Blood and Blood-forming Organs

BLOOD FORMATION

Up to the fifth month of embryonic life blood cells are formed in the liver and spleen. Thereafter normal formation of the red cells, the granular series of white cells and the platelets takes place increasingly in the medullary cavities of bones and from birth onwards is restricted to these sites. During childhood there is a progressive diminution in the amount of red haemopoietic marrow so that in the young adult it is restricted to the heads of the femora and humeri, to flat bones such as the sternum, ribs and ilia and to the vertebrae. The red marrow may extend into the shafts of the long bones when there is an increased demand for blood formation.

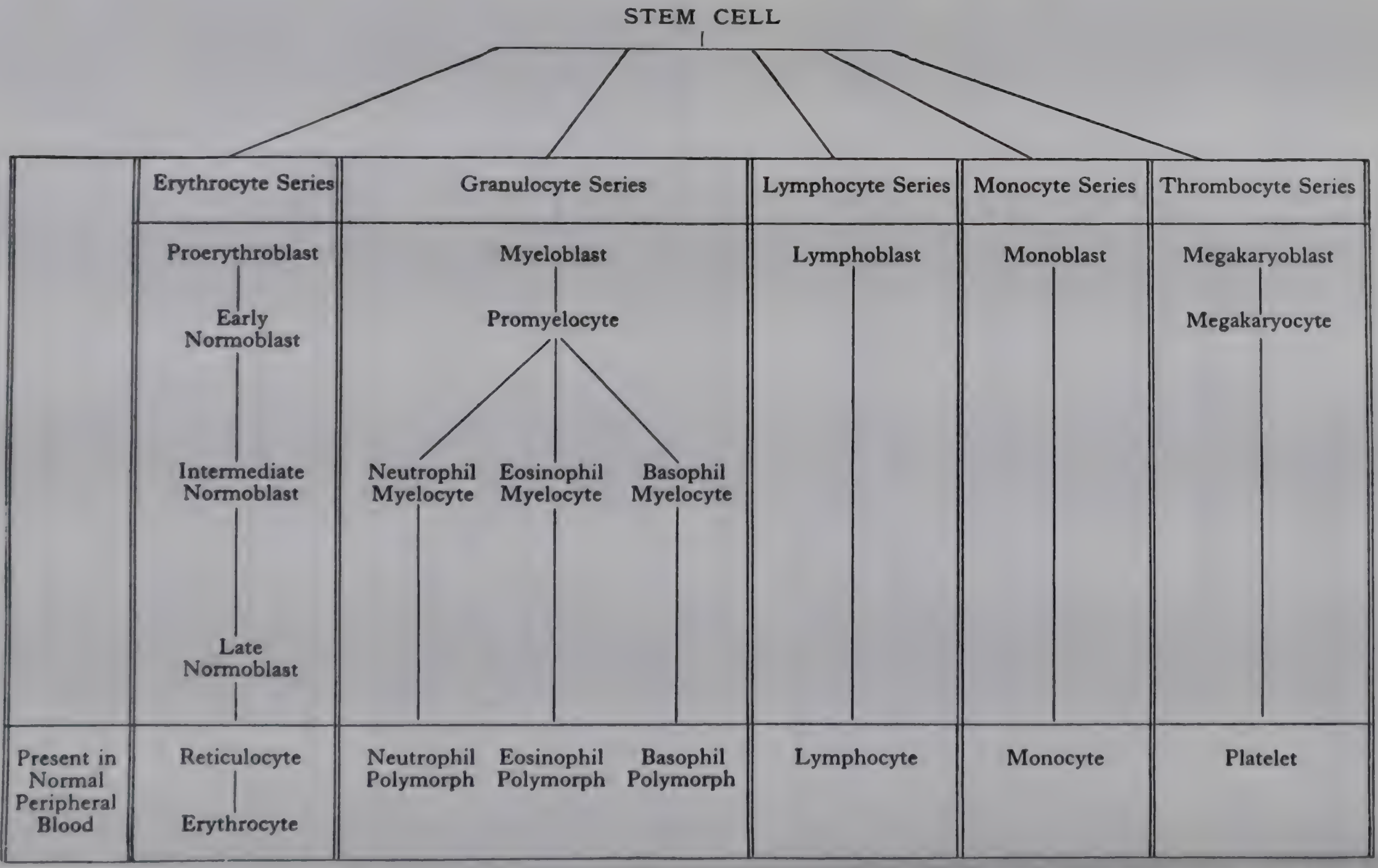
All the cells of the blood are derived from mesenchymal stem cells which belong to the reticulo-endothelial system (Table 12). These are present in the bone marrow; in other sites such as the lymph nodes and spleen they give rise to the non-granular white cells.

1. The Red Blood Cells (Erythrocytes)

The earliest red cell precursor in the marrow is the proerythroblast, a large cell with a nucleolated nucleus and deeply basophilic cytoplasm. Maturation proceeds through the various stages of normoblasts in which there is progressive condensation of the nuclear chromatin and the development of haemoglobin in the cytoplasm. Disappearance of the nucleus completes the formation of the young erythrocyte which is larger than the mature form, shows a faintly bluish colour with Romanowsky stains and still contains fine reticular material, residual RNA from the nucleus, which can be shown by supravital staining with cresyl blue (reticulocyte). The mature erythrocyte stains as an eosinophilic, circular, biconcave disc with a diameter of 7·2 microns. Its shape is adapted to its function in gas transfer and the cell membrane is an elastic and dynamic structure through which water and potassium and sodium ions are passed by active processes, the energy for which is derived from glucose. The red cell membrane carries the blood group characters on its surface. After the first few days of life there are in health no nucleated red cells and less than 1 per cent of reticulocytes in the peripheral blood. The presence of normoblasts indicates excessive or abnormal blood formation or irritation of the bone marrow. An excessive number of reticulocytes reflects increased erythropoiesis. The megaloblast, an abnormal red cell precursor, is considered on page 727.

The number of erythrocytes remains remarkably constant in a healthy individual. There is evidence to suggest that the natural controlling stimulus of erythropoiesis is a hormone-like factor called erythropoietin which is produced mainly in the kidney. It is known that anoxaemia stimulates red cell formation and that those who live at high altitudes have an increased rate of production.

TABLE 12.—ORIGIN AND DEVELOPMENT OF BLOOD CELLS



STEM CELL

	Erythrocyte Series	Granulocyte Series	Lymphocyte Series	Monocyte Series	Thrombocyte Series
	Proerythroblast Early Normoblast Intermediate Normoblast Late Normoblast	Myeloblast Promyelocyte Neutrophil Myelocyte Eosinophil Myelocyte Basophil Myelocyte	Lymphoblast	Monoblast	Megakaryoblast Megakaryocyte
Present in Normal Peripheral Blood	Reticulocyte Erythrocyte	Neutrophil Polymorph Eosinophil Polymorph Basophil Polymorph	Lymphocyte	Monocyte	Platelet

In addition vitamin B_{12}, folate, protein, iron, vitamin C, thyroxine and possibly some trace elements such as copper and manganese are necessary for the continuation of normal erythropoiesis.

Haemoglobin. The role of the erythrocytes depends on their content of haemoglobin which is formed in the bone marrow in the maturing red cells. It is the oxygen transport mechanism of the blood and is also important in the buffering of carbonic acid (p. 199). Haemoglobin is a complex molecule being a conjugate of a protein (globin) with a red pigment (haem), the latter being a combination of a porphyrin with ferrous iron. In normal adult haemoglobin (haemoglobin A) the molecule of globin consists of four paired polypeptide chains, two alpha chains of 141 amino acids and two beta chains of 146 amino acids. Many variants of haemoglobin can occur according to the make-up of the chains, but only three forms are present physiologically. Haemoglobin F which has two alpha chains and two gamma chains is present in the fetus and disappears during the few months after birth. It is replaced by haemoglobin A together with a small percentage of haemoglobin A_2 which combines two alpha chains with two delta chains. It is other variations of the haemoglobin molecule which are associated with the clinical states known as the haemoglobinopathies (p. 737).

Vitamin B_{12} and Folate. These members of the vitamin B complex are important factors in nucleic acid synthesis of many cells of the body including blood cells. In the developing red cell they are required for the maturation of the nuclei of primitive erythroblasts to form normoblasts. If the bone marrow receives an inadequate supply of either vitamin, erythropoiesis changes to an abnormal type characterised by the formation of megaloblasts and there is a diminished output of red cells.

VITAMIN B_{12}. This is the name given to various cobalamins that play a vital role in DNA synthesis. They are present in animal products as distinct from plant products. The active form in the body is probably 5′-deoxyadenosylcobalamin. In man the assimilation of vitamin B_{12} from the lower small intestine is facilitated by the gastric intrinsic factor which is a glycoprotein.

Two forms of the vitamin are used in treatment. The one first used was cyanocobalamin, but it should be replaced as a therapeutic agent by hydroxocobalamin as the latter is less rapidly excreted in the urine and is therefore more effective. The term vitamin B_{12} is used in a general sense but when *therapeutic* agents are being considered it refers to cyanocobalamin. The preferred form, hydroxocobalamin, is vitamin B_{12b}.

FOLATE. This vitamin occurs in varying concentrations in many foodstuffs including both vegetable matter and animal products. Either in the small intestinal lumen or mucosal cells it is broken down to simpler forms by folate conjugase. At some stage after absorption the enzyme dihydrofolate reductase produces reduced forms. Folate is essential for many metabolic processes in the body leading ultimately to DNA formation in cells. The therapeutic agent mainly employed, and given the name folic acid, is pteroylglutamic acid. When a drug such as methotrexate (p. 749) inhibits dihydrofolate reductase, it is usually necessary to employ folinic acid to overcome the metabolic block.

Iron. This is essential for the synthesis of haemoglobin and is present also in myoglobin and certain enzymes such as cytochrome. It is absorbed from the upper small intestine in the ferrous form, and reducing agents such as vitamin C and some amino acids facilitate its absorption in an acid medium. The amount absorbed is largely determined by the activity of erythropoiesis and the level of the iron stores in the body. There is still speculation about the exact mechanism of iron absorption from the intestine. The cells of the small intestinal mucosa are believed to contain a protein named apoferritin which combines with some of the iron to form ferritin. If excessive amounts of iron enter the cell, they are lost to the body because the effete mucosal cell is shed into the gut lumen with its ferritin content. Meantime the iron that is needed has been attached to the iron-binding globulin of the plasma, transferrin, which is not normally fully saturated. The body conserves its iron content so that almost all of that liberated by the breakdown of effete red cells is utilised for fresh haemoglobin synthesis. Hence only about 1 mg daily is lost from the skin and alimentary and urinary tracts. In men this small iron loss is easily replaced by the iron in the food, but balance is more difficult to maintain in women who need to absorb about a further 1 mg daily to cover menstrual blood loss and whose requirements are even greater during pregnancy and lactation.

The iron content of the body gradually increases from 0·5 g at birth to about 5 g in the average adult. Of this some 60 per cent is in the erythrocytes and a reserve is held in the liver, spleen and bone marrow for the replacement of about 25 per cent of the circulating haemoglobin following haemorrhage. This reserve is stored in the body in two forms, ferritin and haemosiderin.

2. The White Blood Cells (Leucocytes)

(*a*) *The Granular Series.* These are so called because of the granules shown by Romanowsky stains in the cytoplasm of the more mature forms. They are derived from the stem cells in the active bone marrow (Table 12) where their earliest recognisable precursors are myeloblasts which have large nuclei containing nucleoli and no cytoplasmic granules. The latter mature to the myelocytes which are smaller cells with coarser nuclei and no nucleoli. About 30 per cent of white cells in the bone marrow are myelocytes. Condensation of the nuclear chromatin proceeds to the formation of metamyelocytes, with kidney-shaped nuclei and finally to the young granulocytes or polymorphonuclear leucocytes which have lobulated nuclei. The older the granulocyte, the more lobes there are in the nucleus and the cells are classified as neutrophil, eosinophil or basophil according to the staining reactions of their granules. The mature neutrophil cells have a high enzyme content and are actively phagocytic to infective organisms which they digest. The products of auto-digestion from cells killed by organisms (pus cells) are potent stimulants of fresh neutrophil formation by the marrow. The eosinophils are also phagocytic and their granules contain histamine. They are concerned in processes involving foreign proteins such as hypersensitivity reactions. The basophil granulocytes are non-phagocytic and have granules containing heparin and histamine.

Mature neutrophil granulocytes account for about 70 per cent of the total leucocytes in the peripheral blood of a healthy adult though a huge reserve of them is held in the marrow and they are present in large numbers in various organs and tissues. Physiological factors which increase their number in the peripheral blood include exercise, emotional stress and pregnancy. Immature granulocytes, represented by metamyelocytes, are found when the production of leucocytes is being stimulated by severe pyogenic infections but in adults the occurrence in the blood of myeloblasts reflects a serious disturbance of marrow function such as leukaemia.

(*b*) *Lymphocytes*. These are mainly derived from stem cells in lymphoid tissue throughout the body though some are found in the bone marrow. The immature form, the lymphoblast, is a large cell with a nucleolated nucleus and so closely resembles the myeloblast that special staining methods are required to differentiate them. From lymphoblasts are derived the large and small lymphocytes both of which are found in the peripheral blood and widely distributed throughout body tissues. It seems that some small lymphocytes are resting cells and are capable of transformation to large lymphocytes in lymphoid follicles. The thymus plays an important role in the production of long-lived lymphocytes which are concerned in the phenomenon of immunocompetence (p. 15). Lymphocytes are mainly concerned with the formation and transport of antibodies (p. 17).

(*c*) *Monocytes*. These are formed from stem cells in the spleen and lymphoid tissue and to a lesser extent in the bone marrow. Immature cells, monoblasts, are large nucleolated forms, very similar to myeloblasts and lymphoblasts and they mature into adult forms with a lobulated nucleus and a cloudy blue cytoplasm containing a few minute red granules. The monocytes are actively motile and phagocytic.

(*d*) *Plasma cells*. These are not found in the peripheral blood in health. They are formed mainly from stem cells in lymphoid tissue and resemble coarse lymphocytes. They are concerned with the elaboration of antibodies (p. 21).

3. The Platelets (Thrombocytes)

These are derived in the bone marrow from megakaryocytes, which are very large cells containing multilobulated nuclei and granular cytoplasm from which the platelets are formed. Platelets are small (2-4 microns) hyaline non-nucleated bodies with blue or purple granules.

Range of Normal Haematological Values

In the newborn the red cell count is approximately 6·0 million per mm^3 and the haemoglobin level about 18 g per 100 ml. Occasional normoblasts and up to 6 to 7 per cent of reticulocytes may be found during the first two to three days of life. By three months the red cell count and haemoglobin concentration have fallen to around 4·0 million per mm^3 and 11 g per 100 ml. Thereafter as erythrocyte production increases the figures rise gradually to the adult range by about the age of 11 years, i.e. red cell count of approximately 4·5 million per mm^3 and haemoglobin of about 14·4 g per 100 ml.

The total white cell count in the peripheral blood at birth is of the order of 15,000 to 25,000 per mm^3, accounted for largely by neutrophil granulocytes. Their numbers fall rapidly in the first two days of life and thereafter until about the age of 4 years lymphocytes comprise the majority of the total white cell count of 4,000 to 10,000 per mm^3. In adults the differential white cell count is constituted as follows:

Neutrophil Granulocytes—60-70 per cent (2,500-7,000 per mm^3).
Basophil Granulocytes—0-1 per cent (0-100 per mm^3).
Eosinophil Granulocytes—1-4 per cent (40-400 per mm^3).
Lymphocytes—23-35 per cent (1,000-3,500 per mm^3).
Monocytes—4-8 per cent (160-800 per mm^3).
Metamyelocytes—4 per cent (160-400 per mm^3).

The erythrocyte sedimentation rate (ESR) is less than 15 mm in 1 hour (Westergren). In the healthy elderly it may be as high as 30 mm in 1 hour.

Other normal haematological values for adults are given on page 1009.

Blood Destruction

Destruction of all formed elements of the blood occurs in cells of the reticulo-endothelial system. The survival time of the mature erythrocytes in the peripheral blood is approximately 110 to 120 days. This is the time as estimated by cross-transfusion experiments and represents the mean life-span. A more practical technique is one in which red cells incorporating ^{51}Cr are transfused and the time taken for half of the radioactivity to disappear is estimated. By this method the half-life of the red cells is 25 to 35 days because of the elution of chromium from the cells. As the cell ages and its enzyme activity declines, its membrane becomes defective so that the cell is removed from the blood and broken down in the reticulo-endothelial system. The degradation of haemoglobin yields iron from haem and this is mostly reutilised by the marrow for fresh haemoglobin synthesis. The iron-free residual pigment biliverdin is converted to bilirubin and carried by the plasma to the liver for excretion.

The life-span of the platelets has also been measured and found to be 9 to 11 days but much less is known about the survival time of the leucocytes. The granulocytes probably last 3 to 4 days but the life-span of the monocytes and lymphocytes is less certain. It appears that some small lymphocytes may re-enter the circulation at intervals for years (p. 17).

Terms relating to Blood Disorders

(*a*) *Anaemia.* This is said to be present when the concentration of haemoglobin in the blood falls below the normal level for the age and sex of the individual.

(*b*) *Microcytosis*. The average diameter of the red cells is reduced. This is commonly found in iron deficiency anaemia.

(*c*) *Macrocytosis*. The average diameter of the red cells is greater than normal. This is seen, for instance, in pernicious anaemia.

(*d*) *Hypochromia*. This exists when the red cells contain less than the normal amount of haemoglobin. They stain less deeply and show central pallor and the mean corpuscular haemoglobin concentration (MCHC) is lower than normal. Hypochromia is commonly associated with microcytosis and is the characteristic feature of iron deficiency anaemia.

(*e*) *Anisocytosis*. This is the name given to inequality in the size of the red cells. It is found in many forms of anaemia but is most prominent in pernicious anaemia. It is an indication of abnormal activity of the bone marrow.

(*f*) *Poikilocytosis*. This name is applied to marked irregularity in the shape of the red cells. It is never present without anisocytosis and usually reflects dyserythropoiesis.

(*g*) *Elliptocytosis*. This means the red cells have an elliptical shape. It is an abnormality of the erythrocytes inherited as a Mendelian dominant and minor degrees of it are quite common and of no pathological significance. In its more severe forms it may be associated with a haemolytic process.

(*h*) *Polychromasia and Reticulocytosis*. Young red cells when stained by the Romanowsky method have a faint bluish colour. A blood film in which such cells are present along with those of normal pink colour is said to show polychromasia. When stained supravitally by cresyl blue the young cells, which are slightly larger than adult erythrocytes, show up as reticulocytes. Polychromasia and reticulocytosis indicate active production of new red cells by the bone marrow.

(*i*) *Punctate Basophilia*. Pathologically damaged young red cells may show several deep blue dots in the cytoplasm when stained by Romanowsky stains. Punctate basophilia may be found in any severe anaemia, but the presence of many cells affected in this way is most commonly seen in chronic lead poisoning, where it may occur when anaemia is slight.

(*j*) *Nucleated Red Cells*. These are usually normoblasts, and are occasionally found when erythropoiesis is very vigorous or more often where there is irritation of the bone marrow, as in leukaemia.

(*k*) *Leucocytosis*. This means an increase in the total number of white blood cells to over 10,000 per mm^3. This may take the form of a polymorphonuclear leucocytosis in which the increase is due to the outpouring of many young neutrophil granulocytes, as occurs in the presence of pyogenic infections such as tonsillitis or pneumonia. Alternatively it may take the form of a lymphocytosis, as is frequently found, for example, in whooping-cough. Infants commonly respond to infections by producing a lymphocytosis.

(*l*) *Leucopenia*. This means a decrease in the total number of white cells below 4,000 per mm^3 and usually involves a reduction only of the granulocytes (granulopenia). Leucopenia is found in tuberculosis, enteric fever, many acute viral infections, undulant fever, etc. Occasionally a leucopenia is found in overwhelming infections and is then a bad prognostic sign.

(*m*) *Eosinophilia*. This is the term used when the number of eosinophil granulocytes exceeds 400 per mm^3. Eosinophilia is found most commonly in infection with worms, in allergic diseases such as asthma, hay fever, urticaria, pulmonary eosinophilias (p. 381), lymphadenoma (p. 753), and in certain skin diseases.

(*n*) *Monocytosis* (*over* 800 *per* mm^3). This is found in, for example, infectious mononucleosis, advancing tuberculosis and malaria.

(*o*) *Thrombocytopenia* means a diminution in the number of blood platelets (normal figure 150,000-400,000 per mm^3). Bleeding tends to occur when the platelet count falls to below 40,000 per mm^3, but there is no exact relationship between the platelet level and a bleeding tendency.

(*p*) *Leucoerythroblastic Anaemia*. This name describes the blood picture in which myelocytes and normoblasts are simultaneously present in the peripheral blood of an anaemic patient. It reflects bone marrow irritation, e.g. in malignant disease (p. 742) or myelofibrosis.

(*q*) *Extramedullary Haematopoiesis*. This term is applied when in an adult patient the bone marrow is replaced by fibrous tissue (*myelofibrosis*) and the production of blood cells takes place in the spleen and liver as in fetal life. This can result in progressive enlargement of the spleen and liver and is accompanied by a leucoerythroblastic anaemia. Extramedullary haematopoiesis occurs not uncommonly in the first year of life when the available bone marrow space is insufficient to allow for an increased demand for blood formation.

DISORDERS OF THE RED BLOOD CELLS

THE ANAEMIAS

A simple clinical approach to the diagnosis of a patient with anaemia is that the condition results from one of the three following causes, though more than one may be present:

1. Diminished production of normal red cells by the bone marrow. This implies failure or suppression of the normal mechanisms promoting erythropoiesis or deficiency of factors required for the maturation of the red cell.
2. Excessive destruction of red cells.
3. Loss of blood, which may be acute or chronic.

In a more detailed classification of the anaemias it must be remembered that those resulting from iron deficiency constitute by far the largest group and it is thus logical to deal with them first. Hundreds of such patients are encountered for every case of megaloblastic anaemia, haemolytic anaemia or pancytopenia. Blood loss results in loss of iron from the body with a consequent deficiency of haemoglobin synthesis. It is also necessary to group together a number of anaemias of uncertain origin in which the specific cause is not known and in which more than one causal factor may be present.

Classification of the Anaemias

I. Anaemias due to Diminished Production of Normal Red Cells

A. Deficiency of Iron

Chronic nutritional hypochromic anaemia.
Post-haemorrhagic anaemia resulting in a relative deficiency of iron.

Hypochromic anaemia due to malabsorption of iron.
Sideroblastic anaemia, a failure of iron utilisation rather than deficiency.

B. DEFICIENCY OF VITAMIN B_{12} OR FOLATE—THE MEGALOBLASTIC ANAEMIAS

Addisonian pernicious anaemia.
Nutritional megaloblastic anaemia.
Megaloblastic anaemia due to pathological conditions of the gastrointestinal tract.
Megaloblastic anaemia in pregnancy.
Megaloblastic anaemia in infancy.
Megaloblastic anaemia complicating haemolytic anaemia or leukaemia.
Megaloblastic anaemia due to various drugs.

C. DEFICIENCY OF VITAMIN C

The anaemia of scurvy.

D. DEFICIENCY OF THYROXINE

The anaemia of myxoedema.

E. PANCYTOPENIA

Primary and secondary.

II. Anaemias due to Excessive Blood Destruction (Haemolytic Anaemias)

A. Due to congenital abnormalities of the erythrocyte. (*a*) Hereditary spherocytosis. (*b*) Hereditary haemoglobinopathies.

B. Due to infective or toxic factors.

C. Due to erythrocyte antibodies. (*a*) Haemolytic disease of the newborn. (*b*) Autoimmune (acquired) haemolytic anaemia. (*c*) Symptomatic haemolytic anaemia. (*d*) Paroxysmal haemoglobinuria.

III. Anaemias of Uncertain Origin

This group includes the anaemias associated with chronic infection, uraemia, rheumatoid arthritis, liver disease and widespread malignant disease.

Clinical Features of Anaemia

Anaemic patients have clinical features which are the direct consequence of the diminished oxygen-carrying power of the blood on the tissues and organs of the body. Their occurrence and severity depend on the degree of anaemia, and especially on the rapidity of its development, but are independent of its type. It is therefore essential to realise that the diagnosis of the type of anaemia cannot be made on the clinical features alone. They are:

Fatigue and lassitude.
Breathlessness on exertion.

Dizziness, giddiness, dimness of vision, headache, insomnia.
Pallor of the skin and, much more significant, of mucous membranes.
Palpitation, tachycardia, cardiac dilatation, functional systolic murmurs.
Anorexia and dyspepsia.
Tingling and 'pins and needles' in the fingers and toes (paraesthesiae). This occurs particularly in pernicious anaemia.
In severe cases there may be oedema of the ankles and basal crepitations.
Angina pectoris (due to myocardial anoxaemia), especially in older patients with coronary artery disease.

I. ANAEMIAS DUE TO DIMINISHED PRODUCTION OF NORMAL RED CELLS

A. Anaemia due to Deficiency of Iron

Chronic Nutritional Hypochromic Anaemia

Aetiology. This is the most common type of anaemia not only in Britain but in every country of the world. It occurs mainly in women of the child-bearing age because of (*a*) the enhanced demands for iron resulting from blood loss from menstruation, and the increased nutritional requirements of pregnancy and lactation; (*b*) insufficient intake of iron in the diet; (*c*) achlorhydria or marked hypochlorhydria which is frequently present and diminishes the absorption of ingested iron. To meet these increased demands women of the child-bearing age need to absorb two or three times the amount of iron required by women past the menopause or by men.

Clinical Features. The symptoms are of gradual onset. In addition to the general features of anaemia described on page 721 there are other features of nutritional deficiency, particularly glossitis, angular stomatitis, koilonychia and atrophy of the mucosa of the pharynx and stomach, giving rise to dysphagia and impairment of gastric secretory function. The glossitis is usually referred to as chronic atrophic glossitis because atrophy of the papillae and mucous membrane gives the tongue a smooth glazed appearance. The atrophy begins at the edges and later affects the whole tongue. As a result the tongue appears moist and exceptionally clean. Koilonychia is the name given to certain changes in the nails first evidenced by brittleness and dryness. Later there is flattening and thinning and finally concavity (spoon-shaped nails). In a small proportion of severe long-standing cases the spleen may be palpable. In anaemia due to deficiency of iron the combination of dysphagia, glossitis and anaemia is known as the Plummer-Vinson syndrome or as sideropenic dysphagia (p. 449).

While paraesthesiae may occur, objective signs of disease of the central nervous system are never found in anaemia due solely to iron deficiency. Blood examination shows a hypochromic, microcytic anaemia. The haemoglobin level may be as low as 4-8 g per 100 ml, with the red cell count between 3 and 4·5 million, and an MCHC of 26 to 30 per cent. Anisocytosis and poikilocytosis are present but not marked. The total and differential white counts show little change from normal. The bone marrow shows a normoblastic reaction. This is illustrated in Plate III which also shows the peripheral blood findings.

Diagnosis. The differential diagnosis from other types of anaemia depends on accurate blood examination. When the presence of hypochromic anaemia has been established a search for possible causative conditions must be undertaken. These include bad diet, haemorrhage, obvious or occult from any site, malignant disease, especially of the alimentary tract, tuberculosis and other infections, and the appropriate examination and investigations must be carried out.

Prognosis. The anaemia is often well advanced, e.g. haemoglobin level 7-8 g per 100 ml before significant symptoms are apparent. If untreated the condition follows a chronic course. The importance of the syndrome is not that it is dangerous to life but that it leads to a loss of efficiency and lowered resistance to infection.

Hypochromic Anaemia in Infancy and Childhood

Aetiology. The following aetiological factors are of importance in explaining the great frequency of anaemia in infants.

(*a*) *Prolonged Milk Feeding.* Breast-fed infants and particularly artificially fed infants who are kept on milk alone without supplements of iron-containing foods become anaemic.

(*b*) *Low Birth Weight.* At birth the full-term baby has about 300 mg of iron stored mainly in the liver and largely accumulated in the last trimester *in utero*. Hence infants born prematurely have low iron stores. The haemoglobin at birth is around 18 g per 100 ml, falling to about 11 g at three months due to a decreased rate of red cell production with a consequently reduced demand for iron. Excess iron from red cell destruction forms a valuable addition to the iron stores at this time. Premature infants or infants of low birth weight (e.g. twins) are at a disadvantage as they have a small circulating red cell mass and derive a reduced amount of iron from red cell destruction. It follows that premature infants will inevitably become anaemic by about the tenth week unless prophylactic iron therapy is given.

(*c*) *Nutritional Anaemia in the Mother.* When a mother is suffering from nutritional iron deficiency anaemia her child's ante-natal stores of iron may be inadequate.

(*d*) *Infections in Infants.* These infections readily interfere with the formation of haemoglobin.

(*e*) *Intestinal Malabsorption* as in gluten enteropathy. This is an occasional cause of hypochromic anaemia in infants or children.

Clinical Features. In infants the symptoms of anaemia are in general much less easy to recognise than in adults but anaemia leads to impairment of general health and vitality and an increased incidence of infections.

Hypochromic Anaemia in Pregnancy

Anaemia is commonly found during pregnancy. The fall in the haemoglobin is due to one or a combination of the following three causes.

(*a*) Iron deficiency anaemia present before pregnancy but exaggerated by (*b*) and (*c*); (*b*) the relative increase of the plasma volume compared to the red cell mass which usually occurs in pregnancy; and (*c*) a deficient intake of iron in relation to the increased demands of the growing fetus. This may be aggravated by anorexia or vomiting.

Anaemia due to Loss of Blood

Post-haemorrhagic anaemia may be acute or chronic.

Acute Post-haemorrhagic Anaemia. The sudden loss of a large volume of blood, 1 litre or more, from, for example, trauma or intestinal bleeding, produces the features of peripheral circulatory failure (p. 251).

The rapid loss of 2-3 litres of blood is usually fatal, whereas an even greater quantity may be lost without causing death if it is spread over a period of 24 to 48 hours. During this period restoration of the circulating blood volume is proceeding by the withdrawal into the blood of tissue fluid. This haemodilution, which takes some hours to develop, is reflected by a fall in the haemoglobin level and red cell count. Hence, immediately after a haemorrhage of, for example, 1 litre in a previously normal person, the blood count will show normal figures, e.g. haemoglobin 14·6 g per 100 ml, r.b.c. 5,000,000 per mm^3, but some hours later when dilution has occurred the figures may have fallen to a haemoglobin level of 11·7 g per 100 ml, and erythrocyte count of 4,000,000 per mm^3. When the circulating blood volume is partially restored, the acute symptoms of shock subside. During convalescence the general symptoms and signs of anaemia may be present. During recovery, red cells are formed more rapidly than haemoglobin and the MCHC falls unless adequate iron is available. New red cell formation is reflected by the appearance of a temporary reticulocytosis of 5 to 10 per cent and there is anisocytosis, poikilocytosis and a leucocytosis of 10,000-15,000 per mm^3. The platelet count may be increased.

Chronic Post-haemorrhagic Anaemia. This results from persistent or repeated loss of small amounts of blood. Frequent causes are menorrhagia, and alimentary bleeding from haemorrhoids, carcinoma, peptic ulcer or ancylostomiasis (p. 976). Alimentary bleeding is also commonly due to aspirin. Persistent blood loss causes a progressive fall in haemoglobin. The clinical and haematological features are similar to those found in chronic nutritional hypochromic anaemia. In addition, the clinical features of the causative disorder will be present.

Diagnosis depends upon the finding of a blood picture of hypochromic anaemia and the discovery of a source of chronic haemorrhage. It is frequently important to test the faeces for occult blood, look for haemorrhoids and perform a full radiographic examination of the alimentary tract.

Prophylaxis and Treatment of Iron Deficiency Anaemia

Prophylaxis. There are two main principles in the prevention of nutritional iron deficiency anaemia in women.

1. The regular consumption of a well-balanced diet containing an adequate quantity of the iron-rich foods.
2. The periodic administration of medicinal iron to women during times of increased physiological demands, e.g. pregnancy, lactation and when menstruation is excessive.

In the prevention of iron deficiency anaemia in infants the maintenance of a normal blood level in the mother is desirable. Premature and unduly small infants should be given medicinal iron as a routine. Iron-containing foods should be introduced into the infant's diet by the third to fourth month and thereafter be progressively increased. Following the control of infection, iron should be given to all infants if the haemoglobin level is reduced.

Treatment

ADULTS. While a diet rich in iron should be prescribed, medicinal iron must also be given. In iron deficiency anaemia, unlike pernicious anaemia and the haemolytic anaemias, there is a depletion of the body's usually considerable iron reserves. In consequence the absorption of iron through the intestinal wall is greatly increased in such patients. The ferrous salts of iron are far more effective in treatment than the ferric salts. A very satisfactory preparation is ferrous sulphate, which should be given in the form of tablets of 200 mg, 1 tablet being taken thrice daily *after* food. Alternative preparations of iron in pill or tablet form are ferrous gluconate, ferrous succinate and ferrous fumarate. All these preparations are equally effective in treatment, but ferrous sulphate is less expensive. Several slow release preparations of ferrous sulphate are available but the cost does not justify their routine use. Intolerance to oral preparations of iron is infrequent if the drug is taken only after meals. If ferrous salts are given in a mixture they must be dispensed in a 50 per cent solution of glucose to prevent oxidation to the ferric state. Proprietary liquid preparations are more palatable but more expensive. A rise in haemoglobin of at least 1 per cent per day is to be expected, and in the average case the blood level is restored to normal in four to eight weeks. In general, synthetic vitamin preparations need not be prescribed if iron medication is supplemented by a well-balanced diet. In particular, expensive preparations containing iron and folic acid should not be used. The addition of trace elements such as copper, manganese and cobalt is of no clinical value. Attention should be paid to sites of gross focal infection, and any source of abnormal blood loss controlled. Apparent lack of response to iron therapy usually means that the patient is not taking the iron.

When the haemoglobin is below 5 g per 100 ml it is usually advisable for the patient to be kept in bed. The decision to transfuse should be based more on the clinical state of the patient than on the haemoglobin level.

After restoration of the blood to normal in a patient who has a chronic iron deficiency anaemia it is desirable to continue iron therapy for at least eight weeks in order to replenish the depleted body stores. Thereafter relapse can usually be prevented by an iron-rich diet. The periodic administration of iron may, however, be required in women of the child-bearing age.

Parenteral Iron Therapy. Commercial preparations of iron for injection can be given intramuscularly or intravenously. The intramuscular preparations include an iron-sorbitol-citric acid complex (Jectofer) and an iron-dextran complex (Imferon). As a general rule such preparations should not be used except when one or other of the oral preparations of iron mentioned above cannot be tolerated or is found to be ineffective. The parenteral route of administration is suitable for the few patients who are genuinely unable to take iron by mouth because of pain, vomiting and diarrhoea, or who are unable to absorb iron because of some disorder of the gastrointestinal tract, e.g. in the malabsorptive disorders (p. 490). Iron given by injection has been recommended for the treatment of the anaemia of rheumatoid arthritis and for the correction of severe anaemia in the late stages of pregnancy and following major operations. It is doubtful whether there is any difference in haemoglobin response to oral or parenteral treatment provided the tablets are taken as prescribed.

The recommended single dose of iron-sorbitol (Jectofer) is 1·5 mg of iron per kg of body weight given daily. A 2 ml ampoule contains 100 mg of iron. It is assumed that about 250 mg of iron are required to increase the haemoglobin level by 1 g per 100 ml of blood. The preparation is administered by deep intramuscular injection and the total dosage of iron should not exceed 2·5 g. Its use is contraindicated in patients with liver or kidney impairment or in those with active urinary tract infection. Oral iron should be discontinued before starting parenteral iron therapy. Jectofer should never be given intravenously.

Iron-dextran (Imferon) is seldom given intramuscularly because of local irritation and since it has been shown to cause sarcomatous change in certain animals. It can be given intravenously by what is known as the 'total dose infusion method' in a suitable diluent. Alarming general reactions may occur.

INFANTS. The treatment of iron deficiency anaemia in infants requires the administration of a liquid iron preparation as well as the introduction of iron-containing food into the diet. The dose should give about 6 mg iron per kg body weight daily. A suitable ferrous sulphate mixture for infants is given in the British National Formulary. Only when parenteral therapy is essential should iron, e.g. Jectofer, be given intramuscularly.

It should be remembered that accidental poisoning from iron can occur if tablets are left within the reach of infants (p. 959).

Treatment of Post-haemorrhagic Anaemia

ACUTE. Treatment consists of bed rest, the administration of sedatives and the correction of the peripheral circulatory failure by the transfusion of sufficient quantities of whole blood or substitutes to restore the blood volume. The cause of the blood loss should be sought and treated. Thereafter iron should be given.

CHRONIC. Treatment involves the arrest of the haemorrhage by appropriate means where possible and the administration of iron and a good diet.

Hypochromic Anaemia due to Malabsorption of Iron

Iron deficiency anaemia commonly occurs in patients with gluten enteropathy, idiopathic steatorrhoea or tropical sprue, or with organic disease of the small intestine, e.g. regional enteritis or tuberculosis. It also occurs subsequent to partial gastrectomy or resection or short-circuiting of the small intestine because of failure of absorption of food iron. Months or years may elapse before the anaemia becomes manifest.

Hypochromic Anaemia due to Abnormal Utilisation of Iron

SIDEROBLASTIC ANAEMIA. Abnormal utilisation of iron with failure of haem synthesis by the marrow may cause a refractory anaemia. In this rare condition there is the characteristic blood picture of chronic iron deficiency anaemia but a failure of response to iron therapy. The serum iron level is high and the bone marrow contains an excess of stainable iron. Primary sideroblastic anaemia is very rare and sometimes sex-linked. The secondary type may be caused by drugs such as isoniazid or be associated with chronic general diseases. Some cases respond to treatment with pyridoxine (p. 164).

B. Anaemia due to Deficiency of Vitamin B_{12} or Folate—The Megaloblastic Anaemias

A deficiency of vitamin B_{12} or folate results in a change of normal erythropoiesis to a megaloblastic marrow (Plate III) characterised by the presence of pathological nucleated red cells which differ from normoblasts. Early megaloblasts are larger than early normoblasts. While the cytoplasm is deeply basophilic in both, the nucleus of the megaloblast has a much more loosely woven network of chromatin. This essential character is seen in megaloblasts even when haemoglobinisation is taking place. Thereafter disintegration and disappearance of the nucleus occurs. The resulting erythrocyte, called a macrocyte, is larger than a normal erythrocyte, has a full complement of haemoglobin, and hence stains uniformly pink; it tends to be more oval than round in shape. Since a certain amount of normoblastic blood formation is proceeding simultaneously in a megaloblastic marrow, the peripheral blood shows a wide variety of cells of different shapes and sizes. Another feature that is often noted is the presence of giant metamyelocytes in the bone marrow. Megaloblastic anaemia may arise in several ways:

1. By a failure in assimilation of vitamin B_{12} consequent on defective production of intrinsic factor by the stomach. This is the cause of Addisonian pernicious anaemia, which is the most common type of megaloblastic anaemia in temperate climates. A similar result occurs after total gastrectomy and may occur after partial gastrectomy or, occasionally gastroenterostomy. Very rarely there

may be an inborn deficiency of intrinsic factor secretion, giving rise to so-called juvenile pernicious anaemia.

2. By an intake of a diet deficient in folate, vitamin B_{12}, or both, leading to nutritional megaloblastic anaemia.

3. By a failure of absorption of folate or vitamin B_{12} as a result of dysfunction, disease, resection or short-circuiting of the small intestine (p. 490).

4. Where there is a blind or stagnant loop of small intestine containing bacteria which apparently utilise vitamin B_{12}, thus rendering it unavailable to the host. The same may occur in jejunal diverticulosis.

5. In pregnancy and infancy. Sometimes in pregnancy, and exceptionally in infancy, there develops a megaloblastic anaemia which invariably responds to folic acid but may be partially or completely refractory to a cobalamin.

6. Infection with the fish tapeworm, *Diphyllobothrium latum*. This condition, found chiefly in Finland, may lead to megaloblastic anaemia particularly in those predisposed to pernicious anaemia because the worm ingests vitamin B_{12} in the alimentary tract of the host.

7. From the administration of various drugs. There are three main groups, (*a*) folate antagonists, e.g. methotrexate and pyrimethamine, which interfere with the dihydrofolate reductase system (p. 715), (*b*) anticonvulsant drugs, particularly phenytoin sodium or primidone, whose method of interference with folate metabolism is uncertain, and (*c*) cytosine arabinoside (p. 749) and certain other agents which interfere with DNA synthesis.

8. Where there is a haemolytic or leukaemic process. The rapidly dividing cells may have an increased utilisation of folate.

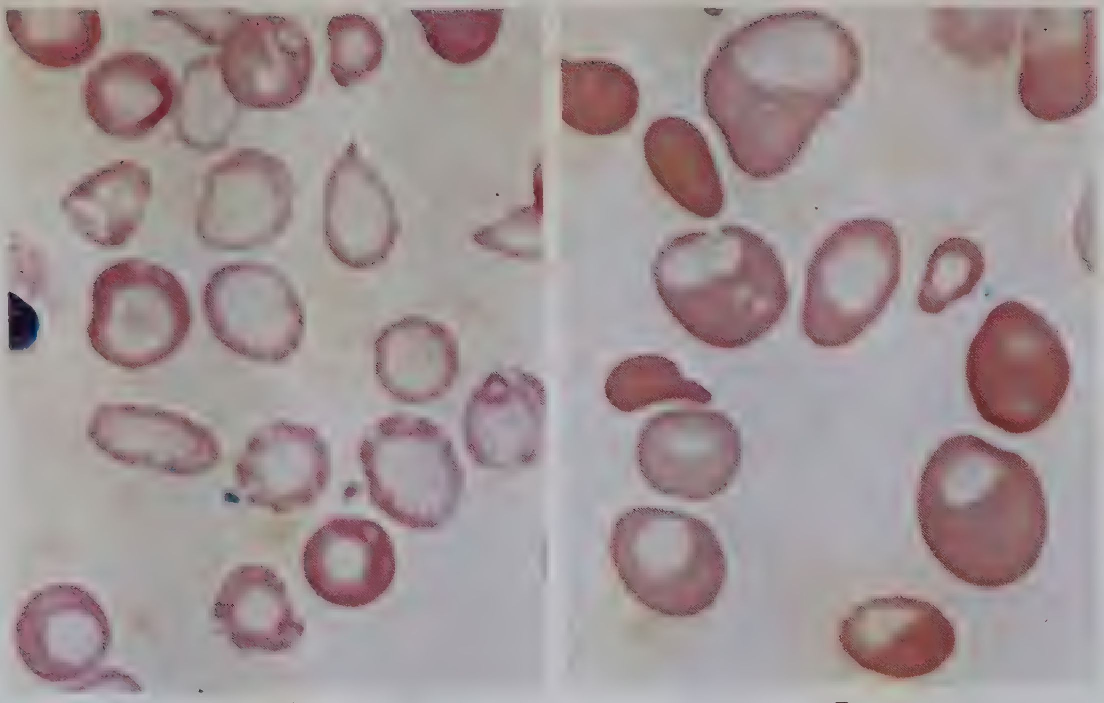
Incidence. In Britain most cases of megaloblastic anaemia are due to intrinsic factor deficiency (Addisonian pernicious anaemia). Of the remainder the megaloblastic anaemias associated with pregnancy or with diseases and disorders of the gastrointestinal tract are the most important. In tropical countries malnutrition and pregnancy are the two main factors concerned in the aetiology of the megaloblastic anaemias.

Addisonian Pernicious Anaemia

The name Addisonian pernicious anaemia should be limited to the group of megaloblastic anaemias which is due to a failure in secretion of intrinsic factor by the stomach other than from surgery.

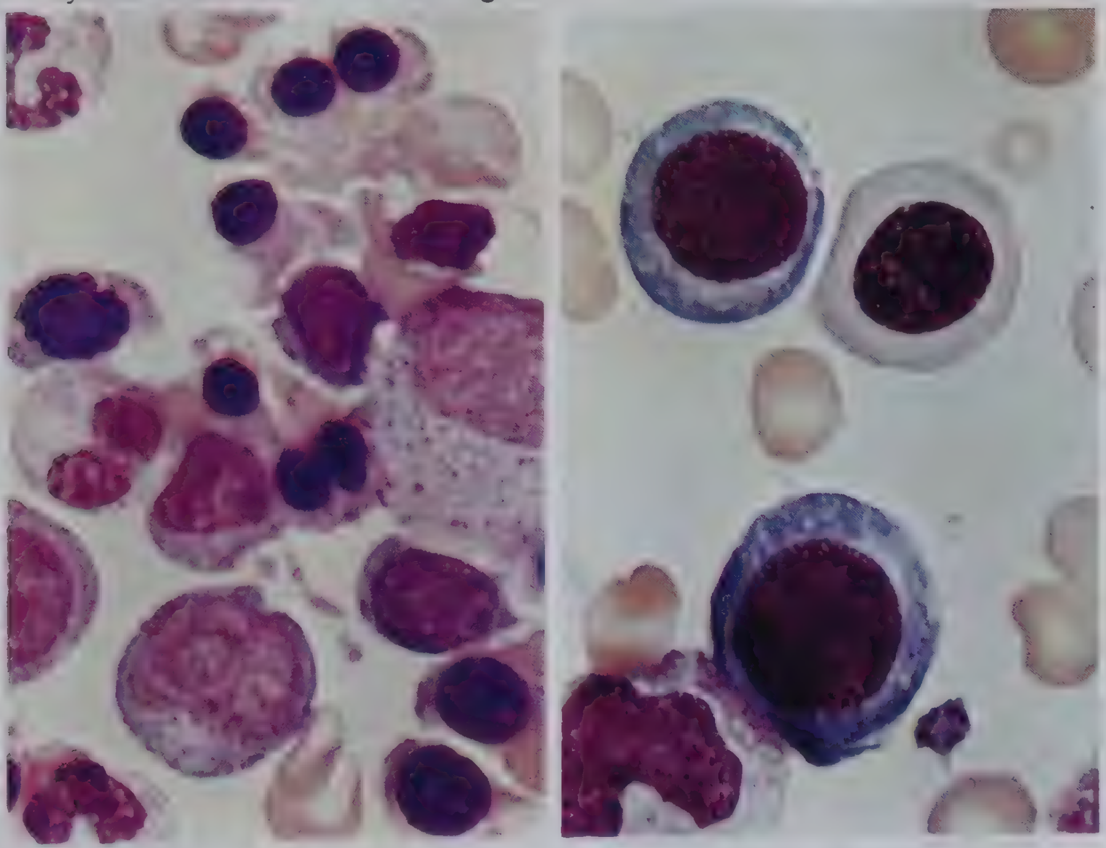
Aetiology. This disease is rare before the age of 30 and affects females more than males between 45 and 65 years of age. The condition is often familial. The gastric mucosa fails to produce the intrinsic factor required for the absorption of vitamin B_{12} from the alimentary tract and there is evidence from the finding of gastric antibodies that an autoimmune mechanism may be responsible for initiating the process.

Pathology. In the stage of relapse there is extension of red bone marrow into the shafts of the long bones. This marrow shows megaloblasts but normoblasts may be present. Polymorphonuclear leucocytes and megakaryocytes are diminished in number. Giant metamyelocytes are a common feature. There



A. Blood film. Iron deficiency anaemia, showing marked hypochromia.

B. Blood film. Pernicious anaemia, showing macrocytosis, anisocytosis and poikilocytosis. The cells are well haemoglobinised.



C. Marrow film. Iron deficiency anaemia, showing hypochromic intermediate and late normoblasts.

D. Marrow film. Megaloblastic series in pernicious anaemia, showing an early megaloblast in the lower half of the field and above it, to the left, an intermediate megaloblast and, to the right, a late megaloblast.

PLATE III

By kind permission of McDonald, G. A., Dodds, T. C., and Cruickshank, B. (1970). *Atlas of Haematology*. 3rd ed. Edinburgh and London: Churchill Livingstone.

is evidence of increased blood destruction—enlargement of the spleen, hyperbilirubinaemia and increased deposition of iron (haemosiderin) in the liver, spleen, kidneys and bone marrow. The gastric mucosa is thin and atrophic. In untreated or inadequately treated cases degenerative changes in the posterior and lateral tracts of the spinal cord may be found.

Clinical Features. The onset is insidious and the degree of anaemia is often great before the patient consults the doctor. In addition to the general symptoms of anaemia (p. 721) there may be intermittent soreness of the tongue and occasionally periodic diarrhoea.

On examination the patient generally appears well nourished despite the fact that weight loss is a common feature. The skin and mucous membranes are pale, and in severely anaemic cases the skin may show a faint lemon-yellow tint. The surface of the tongue is usually smooth and atrophic, but sometimes it is red and inflamed. The spleen is seldom palpable. Gastric analysis invariably shows achlorhydria when histamine or pentagastrin is injected. The urine is found to contain excess of urobilinogen in the relapse stage. In many cases in relapse paraesthesiae occur in fingers and toes—numbness, tingling, 'pins and needles'. Occasionally there are objective signs of involvement of the posterior and lateral columns of the spinal cord (subacute combined degeneration, p. 894), which may rarely be found before the anaemia. Dementia may also occur.

Examination of the stained blood film shows a macrocytic anaemia (Plate III). The mean corpuscular volume is raised and the macrocytes appear fully stained. There is marked anisocytosis and poikilocytosis and many cells are oval in shape. Occasionally in severe cases a few nucleated red cells or haemoglobinised megaloblasts are seen in the peripheral blood. Reticulocytes number less than 1 per cent (except during the commencement of remission). There is leucopenia, the reduction involving only the granulocytes, which are mature, some having an increased number of lobes (more than five) in the nuclei. There is thrombocytopenia, which is usually moderate but can be marked and associated with purpura. The serum bilirubin level is raised.

Diagnosis. It should be realised that the term 'macrocytic anaemia' merely signifies that the number of large red cells in the peripheral blood is increased. It can arise from many causes and the bone marrow may be megaloblastic (as in the conditions mentioned on p. 727) or normoblastic (as in some cases of haemolytic anaemia, pancytopenia, hepatic cirrhosis, myxoedema, leukaemia). The term megaloblastic is reserved for cases in which megaloblasts can be demonstrated in the bone marrow or in the 'buffy coat' of the blood after centrifugation. Pointers to causes of megaloblastic anaemia other than pernicious anaemia include the age of the patient, pregnancy, malnutrition, evidence of malabsorption and the administration of anti-convulsant drugs. In addition to marrow biopsy the serum B_{12} and folate levels should be measured. Thereafter treatment can be commenced in urgent cases without obscuring the diagnosis. In pernicious anaemia a test of gastric acid secretion will show achlorhydria, and, in the Schilling test (p. 490), absorption from the alimentary tract of cyanocobalamin labelled with radioactive cobalt will be impaired but will be corrected by the addition of intrinsic factor available commercially from animal sources. In some areas of Britain, in the elderly, nutritional folate deficiency is as common as Addisonian pernicious anaemia.

Treatment. *General.* The patient may require to be kept in bed until the haemoglobin is about 7 g per 100 ml. The decision to give a blood transfusion is based on general principles concerning the clinical state of the patient. When the haemoglobin level is so low as to endanger life, e.g. under 4 g per 100 ml, it should be seriously considered. In all types of chronic anaemia of sufficient severity to require transfusion the blood must be carefully matched and should be given very slowly, preferably as packed cells, because of the danger of producing sudden cardiac failure. Frusemide (p. 195) should be given simultaneously by mouth or even intravenously with the packed cells.

Specific. Parenteral injection of a cobalamin should be given as soon as the diagnosis is established. Folic acid should *never* be used in the treatment of Addisonian pernicious anaemia as it does not prevent the development of neurological complications, and may possibly precipitate them. Hydroxocobalamin should be given in a dosage of 1,000 micrograms twice during the first week, then 1,000 micrograms weekly until the blood count is normal.

Within 48 hours of the first injection of hydroxocobalamin the bone marrow shows a striking change from a megaloblastic to a normoblastic state. Within two to three days the reticulocyte count begins to rise, reaching a maximum about the sixth day. An increase of 500,000 red cells and 1 g per 100 ml haemoglobin per week can be expected until normal figures are obtained. There is also a rise to normal in white cell and platelet counts.

In some cases the rapid regeneration of the blood depletes the iron reserves of the body so that the haemoglobin fails to rise above 10-11 g per 100 ml and the MCHC falls below normal. To prevent this occurring ferrous sulphate, 200 mg thrice daily, should also be given soon after the commencement of treatment. A combined deficiency of vitamin B_{12} and iron is recognised by the presence of macrocytosis and hypochromia. It is sometimes referred to as a dimorphic blood picture.

When subacute combined degeneration of the cord is present the dose of hydroxocobalamin should be 1,000 micrograms twice weekly and continued at this high level for at least six months.

If a patient diagnosed as having pernicious anaemia fails to respond to the parenteral administration of adequate dosage of hydroxocobalamin, this suggests that the diagnosis is wrong or the preparation used is not potent, or the patient is suffering from one of the other types of megaloblastic anaemia, e.g. megaloblastic anaemia of pregnancy or of idiopathic steatorrhoea, which may be partially or completely refractory to hydroxocobalamin. Such cases respond to folic acid.

Maintenance. It is vital that the patient suffering from pernicious anaemia should continue to receive regular doses of a cobalamin for the rest of his life so that the haemoglobin level and the red cell count are maintained at the normal levels for the sex of the patient. The dose of hydroxocobalamin usually given is 1,000 micrograms by intramuscular injection every four to eight weeks. Theoretically the interval between doses may be longer than this but there is no merit in seeking the minimal effective dose. Blood counts should be done once every year and the assessment should never be made solely on clinical impression or on the haemoglobin level alone. The oral administration of large doses of vitamin B_{12} alone or in combination with intrinsic factor concentrate has not proved satisfactory. When a relative of a patient with pernicious anaemia becomes ill, it is important to remember that he or she may have the same disease.

Prognosis. With the maintenance of a normal blood count by adequate specific treatment the patient remains healthy and has a normal expectancy of life. In the untreated case the disease runs a course which is progressive and usually insidious. Death occurs from anaemia with or without the complication of subacute combined degeneration of the cord, or from intercurrent infection. There is a statistically significant increase in deaths from gastric carcinoma in patients with pernicious anaemia. In cases already suffering from subacute combined degeneration of the cord before treatment is started, adequate therapy restores the blood to normal, prevents further deterioration in the cord changes, and may produce considerable functional improvement if the process is not too far advanced.

Nutritional Megaloblastic Anaemia

This type of megaloblastic anaemia is directly due to the prolonged ingestion of a diet which is deficient in folate, and perhaps vitamin B_{12} and other unknown factors. Such diets are gravely deficient in many nutrients but especially in protein foods, fruit and vegetables. It is of common occurrence in tropical countries, and is very rarely encountered in most areas of Britain although there have been a number of reports of folate deficiency in the elderly, and a few instances of primary deficiency of vitamin B_{12} in immigrant Asian women.

Achlorhydria is not a characteristic feature and lesions of the central nervous system are extremely rare. The peripheral blood shows a macrocytic anaemia unless there is a complicating iron deficiency. The bone marrow is megaloblastic.

Treatment consists of the administration of a well-balanced high protein diet together with folic acid 5-10 mg daily. Injections of hydroxocobalamin alone are frequently ineffective, but it is reasonable to supplement folic acid therapy with injections of hydroxocobalamin. Other vitamins and iron may be required in addition. Maintenance treatment with folic acid is not required if the patient takes an adequate diet.

Megaloblastic Anaemia due to Pathological Conditions of the Gastrointestinal Tract

Megaloblastic anaemia is commonly seen in tropical sprue and idiopathic steatorrhoea (a condition which is frequently a form of gluten-induced enteropathy in adults, page 492). It is due to failure of absorption of folate, of vitamin B_{12} or of both.

Megaloblastic anaemia may occur subsequent to resection or short-circuiting of a large segment of the small intestine. Normally folate is absorbed readily throughout the small intestine, but vitamin B_{12} only from the lower ileum. There is sometimes a complicating defect in the absorption of iron and other vitamins, in which case a dimorphic blood picture results.

The clinical features are those of the underlying alimentary disease together with the general symptoms of anaemia. In addition symptoms and signs of various vitamin and mineral deficiencies are also frequently present (p. 492). Achlorhydria is uncommon and subacute combined degeneration of the cord is very rare. Jejunal biopsy by the oral route and other investigations referred to on pages 488-490 may be of great help if the diagnosis is in doubt.

In tropical sprue and gluten-induced enteropathy there is usually an excellent response to folic acid, which should be given intramuscularly for the first two or three days and orally in a dosage of 20 mg a day thereafter. It is wise to supplement this with 1,000 micrograms of hydroxocobalamin by injection every four to six weeks and, particularly in the tropics, iron by mouth may also be required. When there has been resection or short circuiting of the ileum, the primary deficiency is of vitamin B_{12}.

Megaloblastic Anaemia in Pregnancy

A temporary macrocytic anaemia with megaloblastic reaction in the bone marrow may occur during pregnancy or the puerperium. The clinical features are the same as those of Addisonian pernicious anaemia except that free hydrochloric acid is commonly present in the gastric juice, and subacute combined degeneration does not occur. The factors involved in its causation include increased demands and dietary deficiency, especially of folate and more rarely of vitamin B_{12}.

Prior to modern treatment with blood transfusions and folic acid, there was a mortality of 50 to 75 per cent, death occurring from shock and anaemia aggravated by haemorrhage at childbirth. With modern treatment the prognosis is excellent.

Cases of megaloblastic anaemia of pregnancy usually respond dramatically to the oral ingestion of 10 mg of folic acid daily. If the anaemia is very severe and is not discovered until close to full term, transfusion of compatible blood is indicated in addition. Folic acid therapy should be stopped after the puerperium when the blood level has reached normal, since the disease is self-terminating. Megaloblastic anaemia may recur in subsequent pregnancies. A co-existing deficiency of iron is frequent, and this leads to a dimorphic blood picture. Iron therapy is indicated in such cases. Since there is biochemical evidence of folic acid depletion in about 20 per cent of pregnant women in Britain and because Addisonian pernicious anaemia is rare in this age group, it is reasonable to give folic acid as a prophylactic in pregnancy. This is even more important in tropical countries. In Britain it is convenient to give 1 tablet of a preparation such as Pregaday (Glaxo) daily for prophylaxis. Each tablet of this contains 350 micrograms of folic acid and 100 mg of elemental iron as ferrous fumarate. Numerous alternative proprietary preparations are available.

Megaloblastic Anaemia in Infancy

This type of anaemia occurs infrequently in infants whose diets are markedly deficient in protein, folate and ascorbic acid, and who in addition are suffering from infections and diarrhoea. Although the disease is very rare in Britain it is being recognised in underdeveloped countries as a complication of protein calorie malnutrition (p. 117). The anaemia responds to treatment with folic acid and ascorbic acid. In gluten enteropathy, anaemia is almost invariably due to iron deficiency, but the occasional case with a megaloblastic anaemia will respond to folic acid therapy. Juvenile pernicious anaemia is a rare disease in which there is lack of intrinsic factor, usually without achlorhydria. It should be treated with hydroxocobalamin.

Megaloblastic Anaemia associated with Haemolytic Anaemia or with Leukaemia

Patients with haemolytic anaemia may develop megaloblastic change in the marrow if for some reason, particularly malnutrition, they are deficient in folate. Folic acid therapy is necessary in megaloblastic anaemia if it is a complication of haemolytic anaemia. In acute leukaemia or in the chronic myeloid form the rapidly dividing white cell precursors may deplete the red cell precursors of folate. Treatment with folic acid may cause exacerbations of an acute leukaemic process and thus necessitate more intensive anti-leukaemic therapy.

Megaloblastic Anaemia associated with the Administration of Drugs

When this form of anaemia is due to drugs which interfere with the dihydrofolate reductase mechanism, treatment should be with folinic acid (p. 716). When caused by anticonvulsants, these can be continued provided that simultaneous folic acid therapy is given.

C. Anaemia due to Deficiency of Vitamin C

Anaemia may be found in association with scurvy, a nutritional disease in which there is usually a defective intake of protein and minerals as well as ascorbic acid (p. 149). The anaemia may be normocytic or macrocytic in type but the bone marrow is not megaloblastic unless there is coincidental deficiency of folate or vitamin B_{12}. The cause of the anaemia of scurvy has usually been attributed either to (*a*) loss of blood from the alimentary tract or into the tissues, or (*b*) defective blood formation as a result of ascorbic acid deficiency. It has been shown by radioisotope studies that a haemolytic element may be present and this can be corrected by the administration of ascorbic acid. The administration of vitamin C alone may produce a reticulocyte crisis and a rapid increase of erythrocytes. When associated with an iron deficiency, iron must also be given.

Although frank scurvy is rare in Britain, subscorbutic levels of vitamin C are not infrequently present in cases of nutritional iron deficiency anaemia, especially in elderly men living alone. The giving of ascorbic acid is however generally unnecessary if a well-balanced diet containing fruit and vegetables is prescribed.

D. Anaemia due to Deficiency of Thyroxine

The anaemia of myxoedema is usually moderate in degree and normocytic or macrocytic in type. Accompanying iron deficiency is not uncommon. The clinical picture may strongly suggest pernicious anaemia, but treatment with hydroxocobalamin is ineffective, except in the rare cases with co-existing pernicious anaemia. It is recognised that pernicious anaemia occurs more commonly in patients with myxoedema and that in both conditions there may be evidence of an autoimmune process (p. 642). In the true anaemia of myxoedema, administration of thyroxine produces a slow improvement in the blood level. Associated iron deficiency must be appropriately corrected.

E. Pancytopenia

Primary (Idiopathic) Pancytopenia (previously called Aplastic Anaemia)

This is a rare disease of unknown aetiology. The bone marrow shows a great reduction in all formative elements, and the sample obtained by sternal puncture contains only a few scattered cells in a gelatinous and fatty matrix. The disease may occur at any age but is most common in young adults, or in the elderly.

The clinical features are those of a steadily progressive anaemia with haemorrhage into the skin or from the mucous membranes (due to thrombocytopenia) and fever and necrotic ulcers in the mouth and throat (due to granulopenia). The blood picture is that of a normocytic normochromic anaemia, e.g. haemoglobin 6 g per 100 ml red cell count 2,000,000 per mm^3, MCHC 32 per cent. The reticulocyte count is persistently low. There is leucopenia (2,000-1,000 per mm^3) with progressive diminution in the proportions of granulocytes. The platelet count also falls progressively to figures less than 10,000 per mm^3. The terms 'aplastic' or 'hypoplastic' anaemia are more correctly restricted to cases in which the red cell series is particularly affected. The disease is usually fatal within three to nine months, but complete recovery can occur and cases in childhood may improve spontaneously at puberty.

Secondary Pancytopenia

This may be due to:

1. Idiosyncrasy to certain drugs such as chloramphenicol, phenylbutazone, oxyphenbutazone, indomethacin, sulphamethoxypyridazine, tolbutamide and troxidone, or to certain industrial chemicals and insecticides, chiefly benzol and its derivatives such as trinitrophenol, trinitrotoluene and gamma-benzene hexachloride. It may also result from the use of antimetabolites and cytotoxic drugs which are employed in the treatment of malignant disease.
2. Exposure to X-rays and radioactive substances.
3. Replacement of normal marrow by abnormal cells or fibrous tissue.

There is usually no direct correlation between the dose of a toxic agent and the occurrence or degree of anaemia. Some persons are unduly sensitive. Pancytopenia may develop weeks or months after the cessation of administration of such drugs or exposure to industrial poisons, a point of legal importance in claims for compensation.

Clinical Features. The clinical features and blood changes are similar to those of primary pancytopenia.

The course varies from that of a rapidly progressive fatal condition to a chronic hypoplastic process in which an anaemia of 6-9 g haemoglobin per 100 ml, with a corresponding depression of granulocytes and platelets, may persist for months or years. Complete recovery occasionally occurs, but is rare when chloramphenicol is the causative agent.

Diagnosis of Pancytopenia. The essential haematological findings which serve to distinguish this from other types of blood disorders are: a normochromic anaemia with little anisocytosis and poikilocytosis, absence of reticulocytes or other signs of blood regeneration, granulopenia and thrombocytopenia. A failure to respond to the administration of iron, cobalamin, folic acid and vitamin C strongly supports the diagnosis.

The diagnosis from subleukaemic leukaemia (p. 747) may be very difficult unless the bone marrow is examined. Other blood diseases which should be considered are idiopathic thrombocytopenic purpura and agranulocytosis (pp. 761, 744). It is important to be sure that the patient does not have megaloblastic anaemia.

Treatment. Since the cause of idiopathic pancytopenia is unknown, all that can be done is to support life by repeated whole blood transfusions and give the patient ample amounts of all known haemopoietic factors such as a cobalamin, folic acid, iron and vitamin C. If bleeding is troublesome platelet transfusions may be of great value. In addition prednisolone 60 mg daily may be tried. A synthetic derivative of testosterone, oxymetholone, has given a good response in some children and adults. It is given orally in a dosage of 4-5 mg per kg of body weight daily. It should be continued for several months, but the dosage should be halved when there is evidence of a remission. Treatment with repeated blood transfusions, oral antibiotics and haematinics must be continued for at least six months before being abandoned as recovery occurs in a small proportion of cases. If the cause of secondary pancytopenia can be found and removed the patient may recover provided the bone marrow has not been irretrievably damaged. Injections of dimercaprol (p. 776) should be tried if the condition is due to gold or organic arsenicals. In other respects treatment is the same as for primary pancytopenia.

II. ANAEMIAS DUE TO EXCESSIVE BLOOD DESTRUCTION (HAEMOLYTIC ANAEMIAS)

Destruction of red blood corpuscles either by the cells of the reticulo-endothelial system (intracellular) or within the circulating blood (intravascular) causes anaemia if the degree of haemolysis exceeds the regenerative ability of the bone marrow. The excessive destruction of red cells results in hyperbilirubinaemia with latent or manifest jaundice but without bilirubinuria, hence the name acholuric jaundice. There is, however, excess of urobilinogen in the urine. Haptoglobins are plasma globulins which specifically combine with free haemoglobin to form complexes which are removed by the reticulo-endothelial system. When haemolysis occurs the haptoglobins may be used up more quickly than they are produced and estimations of their level can provide an indication of the degree of the haemolytic process. Rarely in cases of severe haemolysis there is free haemoglobin in the plasma and in the urine. The continuous demand for new red cells results in a constant reticulocytosis, often over 10 per cent. Thus the essential features of any haemolytic anaemia are persistent anaemia, persistent reticulocytosis, hyperbilirubinaemia and excess urobilinogen in the urine and the faeces.

A. Haemolytic Anaemia due to Congenital Abnormalities of the Erythrocyte

(a) Hereditary Spherocytosis (Acholuric Jaundice)

This disease is inherited as an autosomal dominant trait, frequently of variable penetrance (p. 7). The underlying cause is unknown but many of the red cells produced are abnormal in shape, being more nearly spherical than biconcave (microspherocytes). Such cells are unduly fragile and therefore more easily destroyed. This is the fundamental abnormality which is responsible for the clinical and haematological features of the disease.

The symptoms usually appear in childhood but they are often insufficient to cause the patient discomfort. However, moderate pallor and a slight yellow tint in the skin are noticeable. Anaemia and jaundice are mild to moderate in degree, while the spleen is invariably enlarged.

Crises may occur at variable intervals with severe anaemia and jaundice and increased splenic enlargement. At such times the patient complains of weakness and breathlessness, which, in severe cases, may be very marked and associated with rigors, fever and vomiting. The mechanism of the crisis is not fully understood, but it may be precipitated by infection.

Between the crises, blood examination shows a moderate normochromic anaemia, e.g. haemoglobin 10 g per 100 ml, red cells 3,500,000 per mm^3. The reticulocyte count is persistently raised—5 to 20 per cent. Stained films show well-filled red cells, the diameter of which is less than normal, but the thickness of which is increased—microspherocytosis. The red cells are unduly fragile in hypotonic salt solution. The serum bilirubin level is usually from 2 to 4 mg per 100 ml. The urine contains excess urobilinogen but no bilirubin. During a haemolytic crisis the red blood count falls rapidly to a level of 1,000,000-2,000,000 per mm^3 and subsequently the reticulocyte count rises sharply to 40 to 60 per cent or even more. A leucocytosis also occurs. Normoblastic hyperplasia of the bone marrow is found.

The recognition of the existence of a haemolytic anaemia is made on the finding of the characteristic blood picture as described above. The differentiation from other types of haemolytic anaemia depends upon the demonstration of increased fragility of red cells, microspherocytosis, splenomegaly, and especially on the family history of other cases of anaemia and jaundice. Spherocytes may be found in other forms of haemolytic anaemia. If red cells are tagged with ^{51}Chromate and returned to the patient's circulation, their time of survival will be found to be reduced. The Coombs' test (p. 31) is negative in hereditary spherocytosis.

While many patients lead a normal life and die of old age, others suffer from severe episodes of haemolytic anaemia or cholecystitis secondary to the development of pigment stones in the gall-bladder. Such episodes may end fatally.

Treatment. Splenectomy results in striking and usually permanent improvement both in the symptoms and in the anaemia. All authorities are agreed that operation should be advised when the anaemia causes persistent impairment of health, when severe haemolytic crises have occurred, when other members of the family have died from the disease, or where evidence of cholecystitis and cholelithiasis is present. Opinion differs as to the desirability of operation in mild cases with no resulting disability. The operation should be carried out during a period of remission, and in young children should be deferred until school age. Severe haemolytic crises require treatment by blood transfusion. Blood must be matched very carefully and administered by very slow drip, as gross haemolytic transfusion reactions are common in this disease. Iron and other haematinics are of no value. In this type of haemolytic anaemia treatment with corticosteroids is not indicated.

(b) Hereditary Haemoglobinopathies

The hereditary haemoglobinopathies include a wide range of haematological disorders in which, as a result of genetic mutations, there is a disorder of haemoglobin synthesis with the red cells containing in some cases a proportion of one or more abnormal haemoglobins. In some cases the haemolytic anaemia may be so severe as to lead to fatal results, while in others it may be so mild as to cause little or no inconvenience. Examples are thalassaemia, in which there is a failure to synthesise adult haemoglobin with a compensatory rise in haemoglobins F and A_2, and sickle cell disease, a condition most commonly found in Negroes, in which haemoglobin-S occurs. There is no specific treatment and splenectomy is contraindicated. The genetic aspects of the prevention of thalassaemia are discussed on page 13.

The increase of immigration into Britain in recent years of racial groups in whom the haemoglobinopathies are common, and the introduction of relatively simple techniques for identifying abnormal haemoglobins have led to the recognition of considerable numbers of persons suffering from haemoglobinopathies. Very occasionally, refractory iron deficiency anaemia in British subjects without known Mediterranean ancestry may be due to thalassaemia minor.

B. Haemolytic Anaemia due to Infective or Toxic Factors

Haemolytic streptococci, staphylococci and *Clostridium welchii* are the most important micro-organisms which can produce a haemolytic anaemia in man, although such an occurrence is very rare. Malaria is the most important protozoal infection leading to a haemolytic anaemia in the tropics. In blackwater fever (p. 966) a complication of falciparum malaria, severe intravascular haemolysis with haemoglobinuria occurs.

Of the numerous agents which on occasion have been reported to cause haemolytic anaemia, mention should be made of the following: arsenic and its derivatives, lead, sulphonamides, potassium chlorate, naphthalene, phenylhydrazine, methyldopa and nitrofurantoin.

The red cells in some people are deficient in glucose-6-phosphate dehydrogenase activity. Such individuals may develop haemolytic anaemia from contact with beans of the plant *Vicia faba*, or with its pollen (favism), or from taking certain drugs, particularly primaquine or sulphonamides (p. 95). Some of the agents mentioned above may cause haemolysis by this mechanism.

C. Haemolytic Anaemia due to Erythrocyte Antibodies

The most important examples of anaemia in this group are:

(*a*) Haemolytic disease of the newborn.
(*b*) Autoimmune (acquired) haemolytic anaemia.
(*c*) Symptomatic haemolytic anaemia.
(*d*) Paroxysmal haemoglobinuria.

(a) Haemolytic Disease of the Newborn

This disease, previously called erythroblastosis fetalis, occurs in either sex at birth or within the first two to three days. The first-born child in the family is usually healthy, but in successive children the severity of the disease increases and later children may be born dead. Hydrops fetalis is the most severe form, death occurring *in utero*; icterus gravis neonatorum is a dangerous illness but compatible with survival; haemolytic disease of the newborn is the mildest form.

It appears that in most cases the rhesus (Rh) factor is the sensitising agent or antigen. The majority (85 per cent) of people, men and women, have red cells which contain the Rh antigen, D, and these people are said to be Rh-positive. Some of the children of an Rh-positive father and an Rh-negative mother are Rh-positive, since the factor is inherited as a Mendelian dominant. The Rh-negative mother becomes sensitised by the Rh-positive substance contained in the fetal red cells. The maternal agglutinins (antibodies to Rh-positive factor) thus produced penetrate the placental barrier and cause haemolysis of the fetal erythrocytes.

In about 1 pregnancy in 10 the mother is Rh-negative and the fetus Rh-positive. However haemolytic disease of the fetus is very rare in first pregnancies (provided the mother has not previously been sensitised by transfusion) and, fortunately, sensitisation does not occur as often as might be anticipated even in subsequent pregnancies. Indeed the risk of an Rh-negative woman having a baby with haemolytic disease of the newborn in any pregnancy other than the first one is about 1 in 22.

If a mother is Rh-negative and her husband Rh-positive, the maternal serum must be tested for antibodies between the 32nd and 36th week of each pregnancy. If they are found, delivery should be carried out in hospital. If no antibodies are detected the infant will probably escape the disease, but nevertheless the cord blood should be tested for antibodies. If they are present, preventive treatment can be instituted.

Very occasionally an antigen other than D is responsible for the development of haemolytic disease of the newborn.

It must be remembered that an Rh-negative mother who has had an Rh-positive fetus may be sensitised to Rh-positive blood. If she receives a transfusion and Rh-positive blood is given a haemolytic reaction may occur. Consequently all women of child-bearing age or under and all pregnant women who may require transfusion must have their blood typed for Rh factors as well as for the main blood groups.

Clinical Features. The clinical features of haemolytic anaemia of the newborn are those of severe haemolytic anaemia with oedema and enlargement of the liver and spleen. Clinical jaundice is usually absent for 24 hours after birth. Thereafter deep jaundice leading to kernicterus (p. 879) may occur. The severity of the jaundice is largely due to the immaturity of the fetal liver which is unable to conjugate the large amounts of bilirubin with which it has to deal. The blood picture is very striking. The haemoglobin level, which should normally be about 18 g per 100 ml at birth, falls rapidly. Enormous numbers of nucleated red cells (50,000 per mm^3 or more) and reticulocytes 10 to 50 per cent are found in the peripheral blood.

In the severe cases the mortality is 70 to 80 per cent without treatment, death occurring within two weeks, but with exchange transfusion the mortality is low. Spontaneous recovery occurs in the mild cases.

Treatment. Exchange transfusion should be given to all severely affected infants, as this is the only method of treatment that will overcome heart failure in the very anaemic infant and prevent deep jaundice and kernicterus in others. Delay of even a day may prove fatal and hence early diagnosis is essential. Antenatal prediction from tests of the maternal serum for antibodies gives the infant his best chance. In mild cases simple transfusion will be sufficient, and in some instances no treatment is required. It is now believed that the most common cause of primary Rh immunisation may be transplacental haemorrhage during the third stage of labour. The likelihood of an Rh-negative woman developing anti-Rh antibodies is related to the number of Rh-positive red cells present in her circulation immediately after delivery. The injection of gamma globulin containing a high titre of anti-D immunoglobulin into the mother shown to have such cells should be carried out within 72 hours of delivery (p. 41). This will destroy the infant cells that have leaked into the mother's circulation and will prevent the development of haemolytic disease in later babies.

(b) Autoimmune (Acquired) Haemolytic Anaemia

In this form of haemolytic anaemia no family history can be obtained and the fault is believed to lie in the production of autoagglutinins and autohaemolysins which injure the red blood corpuscles (p. 31).

The clinical features are the same as those described for the hereditary type, but the crises are more severe and more frequent and the residual anaemia during remissions of greater degree, e.g. red cell count persistently at or below 3,000,000 per mm^3. Microspherocytosis may not be present and the fragility of the red cells is either normal or but slightly increased. A serological test for immunoglobulin (Coombs' test, p. 31) is positive in acquired haemolytic anaemia, but negative in the hereditary form. It should, however, be realised that the test is not a specific one for the former condition, being positive also in certain uncommon haemolytic disorders, especially in infancy and following the administration of methyldopa.

The prognosis is more serious than in the hereditary form, death in haemolytic crises being more frequent.

It would appear reasonable to try the effect of prednisolone in a dosage of 60 mg daily by mouth for three to four weeks, and if a remission is induced the dose should be reduced to the lowest that will maintain the patient in remission without inducing adverse effects. Should corticosteroids fail initially or if the disorder is particularly severe, transfusion of carefully matched blood is required but the risks of reactions are even greater than in the hereditary form. If corticosteroid therapy fails, splenectomy should be carried out, especially if excessive blood destruction by the spleen can be shown by radioactive isotope studies to be present. The results are not as satisfactory as in hereditary haemolytic anaemia and when splenectomy and corticosteroids fail, immunosuppressive therapy (p. 40) or thymectomy (p. 41) may have to be considered.

(c) Symptomatic Haemolytic Anaemia and
(d) Paroxysmal Haemoglobinuria

Haemolytic anaemia occurs occasionally in association with a variety of diseases such as chronic leukaemia, lymphadenoma, malignant disease, cirrhosis of the liver and infections such as syphilis and tuberculosis. The underlying mechanism is obscure but autoimmune factors contribute. A cold-antibody type of haemolytic anaemia sometimes occurs as a complication about the third week of an attack of virus pneumonia and may be associated with Raynaud's phenomenon (p. 306).

Paroxysmal haemoglobinuria caused by intravascular haemolysis is found occasionally in association with syphilis or after severe exertion. Paroxysmal nocturnal haemoglobinuria is a rare condition of uncertain cause, occurring during sleep, and differs from these others in that frank haemolytic anaemia is not a feature.

Treatment of symptomatic haemolytic anaemia or of the first mentioned types of paroxysmal haemoglobinuria consists of treatment of the underlying condition where possible, and blood transfusions as required. Splenectomy is contraindicated and corticosteroid therapy is not beneficial.

Transfusion with Incompatible Blood

At this point it is appropriate to describe transfusion with incompatible blood as it results in the haemolysis of the infused red cells. Such a situation may arise: (1) when the infused red cells are of the wrong main blood group due to careless typing of the bloods; (2) when the bloods of recipient and donor are of compatible main groups but incompatible subgroups. Direct cross-matching of recipient's serum against donor's cells greatly reduces this risk; (3) from the transfusion of Rh-positive blood to a sensitised Rh-negative recipient.

Symptoms usually begin after only a few millilitres of blood have been given, and if the transfusion is immediately stopped there may be no serious consequences. In severe reactions the patient complains of shivering and restlessness, nausea and vomiting, praecordial and lumbar pain. There is a cold, clammy skin with cyanosis. The pulse and respiration rates increase and the temperature rises to 38-40° C. The blood pressure falls and the patient passes into a state of shock. There is haemoglobinaemia, and possibly even haemoglobinuria; oliguria and even anuria may occur with nitrogen retention due to acute tubular necrosis. Jaundice appears after a few hours. In severe cases the anuria persists and uraemia develops, from which the patient may die. In others diuresis occurs even after several days and the patient recovers. In the majority the acute features subside in 24 to 48 hours.

Prophylaxis involves great care in the typing of blood and direct cross-matching before administration. The first 50-100 ml of any transfusion should be given very slowly and the transfusion stopped at once if any untoward symptoms develop. The patient should be under continuous observation during transfusion. This is especially important when an unconscious patient is being transfused.

Treatment of the established reaction involves giving 100 mg of hydrocortisone hemisuccinate intravenously, and initiating the general treatment of peripheral circulatory failure. When oliguria occurs the measures recommended for its treatment on page 610 must be instituted at once.

III. ANAEMIAS OF UNCERTAIN ORIGIN

More than one causal factor may be operative in some of these conditions.

Infection. Anaemia, which is mild or moderate in degree and normochromic in type may develop secondary to a severe chronic infection, particularly if fever is present. A mild degree of iron deficiency may be found. The response to iron therapy, both oral and parenteral, is usually unsatisfactory unless the infection is eliminated.

Rheumatoid Arthritis (p. 768).

Uraemia. In chronic renal disease anaemia is common but the bone marrow remains cellular until nitrogen retention is very marked, when hypoplasia may be found. It is possible that in advanced renal damage there may be a deficiency of erythropoietin (p. 713) and also a haemolytic component. The anaemia may be normocytic, microcytic or even macrocytic, and hypochromia may be present.

Hepatic Cirrhosis. Here the anaemia is usually macrocytic or normocytic and the marrow macronormoblastic. If megaloblastic anaemia occurs this is probably due to primary malnutrition, and is found particularly in chronic alcoholics with cirrhosis. The occurrence of iron deficiency anaemia suggests gastric or oesophageal haemorrhage.

Malignant Disease. The causes of anaemia in widespread malignant disease are numerous. They include impaired appetite, malabsorption or blood loss from the alimentary tract and occasionally increased haemolysis. Metastases in the bone marrow may cause a leucoerythroblastic anaemia (p. 720).

ERYTHROCYTOSIS AND POLYCYTHAEMIA

In these conditions there is an increase in the number of circulating blood cells in response to a physiological stimulus (erythrocytosis) or as a result of a pathological condition (polycythaemia). Leucocytosis and leukaemia are the equivalent terms for the white cell series.

Relative Erythrocytosis

An increase in the haemoglobin percentage and the red cell count is found in the presence of marked dehydration and haemoconcentration, e.g. after persistent vomiting or diarrhoea, traumatic shock, or extensive burns. There is a decrease in plasma volume and in total circulating blood volume, and the haemoglobin and red cell count fall when the dehydration is overcome.

Secondary Erythrocytosis

This most commonly occurs as a physiological response of the erythropoietic tissue to the stimulus of anoxaemia. Hence it is found in persons living at altitudes over 10,000 ft, in chronic pulmonary disease such as emphysema and in congenital heart disease, especially when an arteriovenous shunt is present. Erythrocytosis may also be associated with high levels of erythropoietin, for example in some patients with renal cysts. It may occur occasionally, for reasons unknown, in cases of Cushing's syndrome, hepatoma and hydronephrosis.

The clinical picture is that of the underlying condition. In contradistinction to what occurs in polycythaemia vera, splenomegaly is rarely present. Blood examination shows haemoglobin 16-20 g per 100 ml, red cell count 6,000,000-8,000,000 (occasionally up to 10,000,000-12,000,000) per mm^3. The PCV is correspondingly raised. Leucocytosis and thrombocytosis are usually absent. The total blood volume is increased.

This variety of erythrocytosis is usually beneficial to the course of the underlying condition and thus requires no treatment.

Polycythaemia Vera (Erythraemia)

This is a rare disease occurring in both sexes mostly about middle age. The cause is unknown. There is overactivity of the haemopoietic tissue, with extension of red marrow throughout the long bones. Microscopically the marrow is hyperplastic, with an increase of normoblasts, myelocytes and megakaryocytes. It is believed that the disease represents a proliferative disorder of the marrow which occasionally progresses to myelofibrosis (p. 720) or to chronic myeloid leukaemia (p. 750). These conditions are probably interrelated and, together with ~~haemorrhagic~~ thrombocythaemia (p. 766), are referred to as the *myeloproliferative disorders*.

Clinical Features. The onset is insidious and the patient complains of throbbing headache, dizziness, ~~tinnitus~~, dyspepsia and fatigue.

In the later stages of the disease, hypertension occurs in about 50 per cent of cases and arterial degeneration is even more common. Owing to the increased platelet count and viscosity of the blood, there is liability to thrombosis. Thus symptoms of peripheral occlusive vascular disease, and vascular accidents, such as coronary thrombosis and cerebral thrombosis, or cardiac failure, may occur. There is also a tendency to haemorrhage from the stomach, urinary tract or uterus.

Examination shows a dusky red and cyanotic facies. The spleen is palpably enlarged and firm in about 75 per cent of cases.

Examination of the blood shows haemoglobin 16-20 g per 100 ml, red cell count 7,000,000-13,000,000 per mm^3, PCV 60 to 70 per cent. The granular white cell count is elevated, and the platelet count is often much increased. The red cells are usually slightly smaller than normal and there may be a relative deficiency of haemoglobin giving a low MCHC. There is a marked increase in blood viscosity due to the increase in red cell mass which is the total volume of red cells in the body and which can be measured by special techniques. In contrast to what is found in chronic myeloid leukaemia (p. 750) the leucocyte alkaline phosphatase score is normal.

Diagnosis depends upon (1) the finding of an increased red cell ~~count~~ and mass, with leucocytosis and thrombocytosis, (2) the presence of splenomegaly, and (3) the absence of conditions described above leading to secondary polycythaemia.

It is wise to carry out an intravenous pyelogram, and to estimate the PaO_2 as the latter is more likely to be low in secondary erythrocytosis of respiratory or cardiac origin.

If a blood count is not carried out the disease may be confused with essential hypertension, psychoneurosis, thrombophlebitis, leukaemia and the various causes of gastrointestinal or urinary haemorrhage.

With modern treatment expectation of life may be normal, but death may occur in a few years from one of the complications, such as the various thrombotic or haemorrhagic episodes mentioned above, or from heart failure. Some cases develop myeloblastic leukaemia and others may terminate as myelofibrosis.

Treatment

1. Venesection. This gives temporary relief, and removal of 500 ml of blood once or even twice weekly can be done to bring the PCV down to about 54 per cent.

2. Irradiation. A satisfactory method of reducing erythrocyte production is by irradiation of the bone marrow. This may be achieved by the administration of radioactive phosphorus (^{32}P), a single dose of 3-7 millicuries of ^{32}P being given by intravenous injection. Further treatment of this nature will depend upon the response to the first dose.

3. Chemotherapy. Busulphan (p. 751) in an initial dosage of 2-4 mg daily followed by a maintenance dose of 2 mg once or twice weekly has been found effective. It has been suggested that patients treated in this way are less likely to develop acute myeloid leukaemia than after treatment with radioactive phosphorus. The antimalarial drug pyrimethamine is a folate antagonist which may be used if other therapy is not available or is contraindicated.

DISORDERS OF THE WHITE BLOOD CELLS AND THE RETICULO-ENDOTHELIAL SYSTEM

Agranulocytosis

Agranulocytosis is a serious disease characterised by marked leucopenia with great reduction in, or absence of, neutrophil granulocytes.

Aetiology

1. In most cases the cause is an idiosyncrasy or sensitisation to, or poisoning by, a variety of drugs. Among these the most important are amidopyrine, chlorothiazide, chlorpromazine, chlorpropamide, imipramine, phenindione, phenylbutazone, oxyphenbutazone, streptomycin, various sulphonamides and thiouracil derivatives. Exposure to insecticides should also be considered.
2. In some cases there is no discoverable cause—idiopathic agranulocytosis.
3. It may follow excessive irradiation or the use of cytotoxic drugs or anti-metabolites (p. 749).
4. Agranulocytosis is found as an integral part of pancytopenia (p. 734), leukaemia and some cases of hypersplenism (p. 756).
5. It occurs, rarely, in severe infections.

Pathology. In most cases the bone marrow shows a virtual disappearance of the granular cells and their precursors. In some the marrow contains many early myelocytes, with few mature forms—an arrest of maturation. In the cases in group 4 the appearance of the bone marrow is that of the underlying blood disease.

Clinical Features. There may be a history of exposure to one of the noxious agents mentioned above. The onset may be either sudden or gradual. In the acute and severe cases the condition begins with sore throat, fever and often rigors which are followed by great prostration. There is rapidly advancing necrotic ulceration in the throat and mouth, with little evidence of pus formation. In fulminating cases the patient dies in a few days from toxaemia and septicaemia. In less acute cases there may be a preliminary period of malaise and weakness.

Blood examination may show little alteration in the haemoglobin or red cell count. There is marked leucopenia, usually below 2,000 per mm^3, and falling to 500 per mm^3 or less. The percentage of granulocytes falls rapidly until none may be found.

A chronic type has been described in which there is a persistent or recurring leucopenia with granulopenia (e.g. white cell count 2,000-2,500 per mm^3, granulocytes 20 to 30 per cent). Rarely the neutropenia occurs in cycles of three weeks (cyclic neutropenia). In such cases the symptoms are chiefly malaise, low grade fever and sore throat often without ulceration.

Diagnosis. This depends upon the examination of the blood. The condition may be confused with diphtheria and Vincent's angina. Whenever necrotic ulcers are found in the mouth or throat, it is important to carry out an examination of the blood and bone marrow to eliminate primary blood diseases like pancytopenia and leukaemia. Enquiry must be made to determine whether or not there has been exposure to one of the drugs listed above.

Prophylaxis. All the drugs mentioned at the beginning of this section should be regarded as potentially dangerous and should be carefully employed. The patient should be warned to report to his doctor if he feels unwell and feverish or if he develops a sore throat.

Treatment. On the first appearance of sore throat and fever the administration of any of these drugs should be stopped and a white cell count carried out. A blood culture should be obtained and antibiotics should be administered preferably by the oral route, e.g. ampicillin (p. 97), and fresh blood should be transfused. Even the fulminating cases may be saved by these means, but no cure will result unless the formation of granulocytes is resumed. This usually occurs within two to three days if infection is controlled and the cause has been removed. Should improvement not occur, the patient should be given blood transfusions. Careful nursing in isolation is required with adequate diet and extra vitamins. Regular toilet of the mouth will contribute greatly to the patient's comfort. Dimercaprol injections should be given if agranulocytosis follows the administration of gold salts or organic arsenicals.

Prognosis. In severe cases the mortality is very high, but in chronic or recurring cases recovery is common. Spontaneous resumption of granulocyte formation frequently occurs, especially if the leucotoxic drug is withdrawn, and this gives rise to difficulty in assessing the value of therapy.

Infectious Mononucleosis

(Glandular Fever)

This is a benign acute infective disease most probably due to the Epstein Barr virus as antibodies to this agent can be found in the serum of patients who have recovered from the disorder. It occurs chiefly in children and young adults of either sex both sporadically or in epidemics. The condition is mildly infectious, the incubation period probably being 5 to 10 days.

Clinical Features. The most common presenting features are tiredness, malaise and generalised pains in muscles, headache, pyrexia and enlargement of superficial lymph nodes. An early sign may be the occurrence of petechial haemorrhages at the junction of the hard and soft palate and this is frequently followed by sore throat with or without exudate. The glandular enlargement may not occur until the third week. A maculopapular rash often appears during the first 10 days in adults. The spleen may be enlarged but seldom extends much below the costal margin. It is soft and not tender. Pain in the right iliac fossa may result from mesenteric adenitis.

There is usually no anaemia and in the early stages the white cell count is frequently normal or low. However in the first few days there may be an increase in the proportion of granulocytes, but thereafter the characteristic increase in non-granular white cells appears, amounting to 60 to 80 per cent of the total white cell count. These include ordinary lymphocytes, ordinary monocytes and 'atypical' lymphocytes (large cells with blue-staining often foamy cytoplasm and nuclei with coarse chromatin, which may be oval, kidney-shaped or have a pseudopodial appearance). The proportions of these cells vary greatly in different cases but immature leucocytes are not present. The total white cell count is commonly 10,000-20,000 per mm^3.

Heterophile antibodies develop in the serum of patients with infectious mononucleosis and their demonstration forms the basis of valuable diagnostic tests. After the first week of the illness the Paul-Bunnell reaction becomes positive in titres of 1 in 200 or more in over 80 per cent of cases and may remain positive for many weeks. Absorption techniques are necessary to distinguish the specific antibodies of infectious mononucleosis from those of serum sickness which may also cause a positive reaction. The Wassermann reaction also may be falsely positive in infectious mononucleosis. A simple and rapid slide test known as the 'Monospot Test' is now commonly used as a screening procedure in infectious mononucleosis and is quicker and more sensitive than the Paul-Bunnell reaction. It has also been observed that if patients with infectious mononucleosis have been given ampicillin to treat what was thought to be a bacterial throat infection, they develop, in over 90 per cent of instances, a skin eruption due to the drug within two to three days. The reason is not understood but it is unsafe to give ampicillin as a diagnostic test as laryngeal oedema may occur in some cases.

Diagnosis. During the invasive phase, especially in children, the disease may be confused with the various exanthemata, tonsillitis and diphtheria. Distinction must be made from leukaemia in which there is persistence of the clinical features, including lymph node enlargement, and in which the marrow biopsy is characteristic and the Paul-Bunnell test is negative; and from lymphadenoma in which the lymph node enlargement is persistent and progressive and the peripheral blood does not show the characteristic 'atypical' lymphocytes. The secondary stage of syphilis must also be excluded. In young people, the condition in a milder form may cause general ill-health and be overlooked unless a blood film is examined. In contrast in severe cases there may be features of lymphocytic meningitis or mild encephalitis. It should be noted that in toxoplasmosis (an infection with the protozoon *Toxoplasma gondii*), and in cytomegalic inclusion disease, there may be enlargement of lymph nodes and changes in the blood picture similar to those found in infectious mononucleosis.

Treatment. This is symptomatic, the patient being kept in bed during the febrile period. Corticosteroid therapy may be helpful if the constitutional symptoms are severe.

Prognosis. Although recovery is invariable, some patients may be ill for weeks or months with intermittent fever, sweats and debility. Very occasionally hepatitis or rupture of the spleen may occur. Sometimes there is thrombocytopenia or haemolytic anaemia of the autoimmune type.

Seminar

The Leukaemias

The name leukaemia is given to a group of diseases characterised by an abnormal and excessive proliferation of leucopoietic tissues throughout the body, and usually associated with an increase in the total number of circulating white blood corpuscles, among which immature forms occur. Though the course of the disorder may vary considerably from a few weeks to several years, the leukaemias are all invariably fatal, death being due to progressive anaemia, haemorrhage or intercurrent infection.

The cause of leukaemia is not known. In some ways the condition behaves as a neoplastic process, as there is uncontrolled proliferation of cells and the development of foci of leucocyte formation in organs other than the bone marrow and lymph nodes. However, the process appears to start simultaneously throughout the leucopoietic tissue and the cells show no truly invasive properties as do malignant tumour cells. These features are more suggestive of a generalised cellular disturbance. Cytogenetic studies have shown that chromosomal abnormalities are present in some leukaemic cells. Furthermore it is recognised that exposure to ionising irradiation may produce chromosome damage and that such irradiation may in some instances be an aetiological factor in the initiation of leukaemic change. The possibility of a viral aetiology of leukaemia continues to attract widespread attention.

The leukaemic process may affect the formation of any one of the granulocyte, lymphocyte or monocyte cell series. In acute leukaemia, of which there are three varieties according to the cell line involved, the disorder pursues a rapidly progressive course with excessive production of the most primitive precursor cells referred to as 'blast' cells. In chronic myeloid and chronic lymphatic leukaemia the over-production affecting the granulocytic or lymphatic series is a slower and more benign process reflected in the appearance of more mature cells in the blood. The term subleukaemic leukaemia (sometimes called aleukaemic leukaemia) is applied to any form of leukaemia in which the total white cell count in the peripheral blood is not increased, though the differential blood count may show the presence of immature circulating leucocytes and bone marrow examination is essential to establish the diagnosis. A rare variation of acute myeloblastic leukaemia associated with an extraordinary proliferation of red cell precursors in the marrow and with large numbers of normoblasts in the peripheral blood is referred to as di Guglielmo's disease or erythraemic myelosis.

Acute Leukaemia

Owing to the similarity in the clinical picture, it is convenient to consider all forms of acute leukaemia together. Acute lymphoblastic leukaemia is in general the most common variety, and is the most frequent type of leukaemia in children, occurring in the subleukaemic form. It is the most common cause of death from malignant disease in childhood. Acute myeloblastic leukaemia and the least common variety, monoblastic leukaemia, occur at all ages. Both sexes are affected. The pathological changes are similar to those found in the chronic forms (pp. 750, 751), but myeloblasts, lymphoblasts or monoblasts predominate in the respective types. The spleen and lymph nodes do not usually become as large as in the chronic forms.

Clinical Features. The disease may begin insidiously but the clinical onset is usually abrupt. There is fever, malaise and a rapidly advancing anaemia. Epistaxis, spongy bleeding gums or other haemorrhagic manifestations, including purpura, are common and are due largely to thrombocytopenia. Sore throat and ulcers in the mouth or pharynx are frequent, due to reduction in normal polymorphonuclear leucocytes. Hypertrophy of the gums is often noted in monoblastic leukaemia. Muscular and joint pains may occur. The spleen and often the liver are enlarged in the later stages. The cervical lymph nodes may be enlarged secondary to pharyngeal sepsis, but in the lymphatic form increase in size of these and other lymph nodes is a common early feature.

Blood examination shows a profound and increasing anaemia of normochromic type. Normoblasts and increased numbers of reticulocytes are frequently seen in the peripheral blood, due to disturbance of the erythropoietic tissues in the bone marrow by leukaemic infiltration. Thrombocytopenia is common with a prolonged bleeding time. The white cell count may be normal or low but is usually increased to 20,000-50,000 per mm^3. Immature ('blast') cells comprise 30 to 90 per cent of the white cells. The distinction between the different types of primitive white cells is often difficult, but in acute myeloblastic leukaemia myelocytes and granulocytes, in acute lymphoblastic leukaemia lymphocytes, and in monoblastic leukaemia monocytes, form most of the remainder of the white cells and suggest the diagnosis.

The bone marrow shows a marked predominance of the appropriate primitive white cell to the almost complete exclusion of all normal marrow cells.

Diagnosis. In the early stages the condition may be confused with infective illnesses, such as miliary tuberculosis, acute rheumatic fever, and infectious mononucleosis, this last being most important in differential diagnosis. Pancytopenia, agranulocytosis and the haemolytic anaemias may also be simulated. The rapidly advancing anaemia, the eventual enlargement of the spleen, liver or lymph nodes and the finding of immature white cells in the peripheral blood suggest the diagnosis and this is established by marrow biopsy, which shows a large excess of primitive white cells of the appropriate type. The subleukaemic form may give particular difficulty since the total white count is normal or low, but immature cells are to be found in the peripheral blood on careful search or in buffy coat smears, and marrow biopsy reveals the typical picture of acute leukaemia.

Treatment. While there is no known cure for leukaemia there have been great changes in the approach to intensive palliative treatment in recent years, with increasingly encouraging results especially in the acute lymphoblastic form in childhood. It must be emphasised that the best results have been obtained in centres experienced in coping with the complex problems of the chemotherapeutic regimes involved. The details of the latter in current use are beyond the scope of a short textbook chapter and what follows is a brief account of the types of drugs employed and an indication of the ways in which they may be used.

Mention must first be made of the corticosteroid prednisolone which has a specific lympholytic effect in addition to an action on capillaries which reduces the bleeding tendency associated with thrombocytopenia. It is thus a most important drug in the induction of a remission in cases of acute lymphoblastic leukaemia and is given in the other acute varieties when the platelet count is low. Most of the other drugs used in this form of chemotherapy act by interfering with nucleic acid synthesis and they affect not only the dividing leukaemic cells but also normal cells so that severe haemopoietic depression and other serious side-effects can be produced. Mercaptopurine, thioguanine, methotrexate and cytosine arabinoside are examples of antimetabolites; vincristine is a plant alkaloid, and daunorubicin an antibiotic, while cyclophosphamide is one of a large group of alkylating agents which also include the nitrogen mustards. These compounds act in various ways to interfere with cell mitosis. Asparaginase is an agent which destroys asparagine on which some leukaemic cells are dependent. Radiotherapy is of no value in acute leukaemia except in the eradication of leukaemic cells in the brain in children. Immunotherapy, e.g. with BCG vaccine is sometimes used to provoke the normal body immunity mechanisms to destroy leukaemic cells remaining after chemotherapy.

Supportive treatment of patients with acute leukaemia is important because of the effects of the disorder and the side-effects often induced by chemotherapy. Blood transfusion is given to correct anaemia, platelet concentrates may be required to arrest a bleeding tendency not prevented by prednisolone and antibiotics may be necessary to combat infections associated with pancytopenia and immunosuppression.

The aim in treatment is to induce a haematological remission by destroying the maximum number of leukaemic cells and, when the patient's general state has improved, to attempt to eradicate any remaining leukaemic cells by intensive chemotherapy. Combined drug therapy is always used to attack the cells in different ways simultaneously. Thus in a child with acute lymphoblastic leukaemia, prednisolone and vincristine are given to induce a remission which can be expected in 3 to 4 weeks. Thereafter intensive chemotherapy is started using cyclic courses of combined mercaptopurine, methotrexate and cytosine arabinoside which are repeated for three years alternating with short re-induction courses. Since these drugs do not cross the blood-brain barrier and leukaemic cells in the central nervous system may survive to cause relapse of the condition, radiotherapy to the brain of the child along with intrathecal injections of methotrexate are also given in an attempt to eradicate the leukaemic process. Continuous remissions of more than 3 years are being achieved by measures such as these with expectation of further improvement as coordinated trials of new drug regimes proceed. The results of treatment in the other varieties of acute leukaemia in children and in all types in adults are at present much less impressive than those indicated above. In the acute myeloblastic and to a lesser extent in the acute monoblastic types, daunorubicin has proved valuable in producing a temporary ablation of the bone marrow for the purpose of initial treatment and its use along with cytosine arabinoside and other drugs has led to prolonged remissions in an increasing number of cases.

Prognosis. The condition is fatal and unless the course is modified by chemotherapy, death occurs usually within a few weeks, due to anaemia, secondary infection or haemorrhage. Temporary short remissions may sometimes occur spontaneously in the monoblastic variety.

Chronic Myeloid Leukaemia

The disease occurs chiefly between the ages of 35 and 60 years and is equally common in males and females.

Pathology. There is extension of the marrow through the long bones. The marrow is grey and gelatinous and is crowded with myelocytes and young polymorphonuclear leucocytes. Leukaemic infiltrations occur in the liver, spleen and lymph nodes, and in most organs throughout the body.

Clinical Features. The onset is insidious and the clinical features are very varied. There may be slowly advancing anaemia with loss of weight, dragging discomfort in the left upper quadrant of the abdomen due to the great enlargement of the spleen, and enlargement of the abdomen. Attacks of acute left upper abdominal pain may develop when infarction occurs in the spleen. Epistaxis or other haemorrhages may occur in the later stages.

The spleen is found to be much enlarged, occasionally extending across the midline and reaching below the umbilicus. It is firm and smooth and may be tender if infarction has recently occurred. The liver is also enlarged but the lymph nodes are usually of normal size.

Blood examination shows an anaemia of normocytic, normochromic type which increases as the disease progresses. Normoblasts are often found. The white cell count is greatly increased to 50,000-500,000 per mm^3 or more and consists almost entirely of young granulocytic cells, myelocytes and occasional myeloblasts. In the later stages the appearance of an increasing number of myeloblasts indicates the approach of a terminal acute phase. The platelet count is often high initially but thrombocytopenia gradually develops.

Diagnosis. This depends upon the finding of the characteristic blood picture. Marrow biopsy may be required to exclude other conditions causing a leuco-erythroblastic blood picture (p. 720). The granulocytes of chronic myeloid leukaemia are deficient in alkaline phosphatase and this is the basis of a staining reaction to differentiate them from normally developing granulocytes. In a high proportion of cases a characteristic abnormality of the 22 chromosome, the Philadelphia chromosome (p. 12), is found in the myelocytes. The relationship to other myeloproliferative disorders is described on page 743.

Treatment. Effective palliative treatment can restore most patients to a period of symptom-free life. The method of choice is by chemotherapy using the alkylating agent, busulphan (Myleran). It is given orally in a commencing dose of 4 mg daily and can bring about a temporary but satisfactory clinical and haematological remission in a high proportion of cases. Subsequent maintenance dosage, e.g. 2 mg daily, is continued and regulated according to the results of frequent blood examinations and the general state of the patient. It must be emphasised that all such drugs are capable of producing severe haemopoietic depression and their administration requires careful haematological supervision. The too rapid destruction of abnormal white cells may cause a rise in blood uric acid and even uric acid nephropathy. Allopurinol (p. 785) can be used to prevent this complication. Blood transfusion may be necessary to correct increasing anaemia and in some cases, where there is evidence of haemolysis, corticosteroids may be beneficial.

Radiotherapy, given as a course of localised splenic irradiation, reduces the size of the spleen and brings about a fall in the abnormal white cell count with a simultaneous improvement of the anaemia and general health. The dosage is controlled by frequent blood examinations and treatment is stopped when the white cell count falls to about 20,000 per mm^3 or if the platelet count drops excessively. Further irradiation is needed when relapse occurs, usually after about nine months, and thereafter courses may be required at shorter intervals.

Prognosis. The disease pursues a chronic course with increasing general features of anaemia. With treatment the average duration of life from the time of diagnosis is about three years, though some patients live longer. The terminal acute stage is indicated by the appearance of an increased number of myeloblasts, up to 10 to 15 per cent or more, by marked anaemia and by haemorrhages.

Chronic Lymphatic Leukaemia

This is the commonest variety of leukaemia and occurs much more commonly in males than in females and in the age period 45 to 80 years. L/C-1

Pathology. There is moderate enlargement of lymph nodes and other lymphoid tissue throughout the body, the normal structure being replaced by a mass of lymphocytes. The spleen and liver are moderately enlarged and show lymphocytic infiltration. The bone marrow becomes progressively infiltrated with lymphocytes, which eventually replace the erythropoietic and myeloid tissue.

Clinical Features. The onset is very insidious and in contrast to chronic myeloid leukaemia the development of anaemia tends to be much slower and the presenting feature is usually the finding of firm rubbery, discrete and painless lymph nodes in the cervical, axillary and inguinal regions. The spleen is palpable but is usually smaller than in chronic myeloid leukaemia. The liver may also be enlarged. Haemorrhagic manifestations are much less common than in the chronic myeloid variety, but in widespread lymphoproliferative disorders there is an increased tendency to recurrent infections due possibly to altered immunity mechanisms.

Peripheral blood examination usually shows a mild but increasing anaemia, though normoblasts are rarely found. Haemolytic anaemia may occur. The white cell count is greatly increased, up to 500,000 per mm^3. Of these cells about 95 per cent are lymphocytes, which are predominantly of the small variety. Lymphoblasts are rare except in the terminal stages. The platelet count is usually low and may fall below 100,000 per mm^3.

Diagnosis. When the white cell count is very high the recognition of the disease is easy by examination of a blood film. When the white cell count is below 30,000 per mm^3 marrow biopsy is essential. Chronic lymphatic leukaemia must be distinguished from (1) *lymphadenoma* and other forms of reticulosis in which there is no characteristic blood picture and which usually occur in a younger age group; (2) *infectious mononucleosis*, which has an acute febrile onset, in which the enlarged lymph nodes are soft and may be tender, the proportion of monocytes is increased, the lymphocytes are atypical and the Paul-Bunnell test is frequently positive; and (3) *tuberculous cervical lymphadenitis*, which occurs in young people and in which there is usually no enlargement of lymph nodes in other areas or of the spleen.

Treatment. Elderly patients with chronic lymphatic leukaemia may remain in relatively good health with little or no anaemia for several years. When treatment becomes necessary, or in younger patients, chemotherapy may be used. In general the response in chronic lymphatic leukaemia is less dramatic than in chronic myeloid leukaemia, and increasingly frequent courses of treatment are required. The most satisfactory chemotherapeutic agent at present available is the alkylating agent chlorambucil. The suggested dose is 0·1-0·2 mg per kg of body weight given daily in tablet form for two to eight weeks depending on the haematological response. Corticosteroid therapy may be of value where there is evidence that haemolysis is contributing to the anaemia. Radiotherapy may also be used in treatment, either as localised irradiation to shrink a large mass of lymph nodes or as splenic irradiation in cases with gross splenomegaly.

Prognosis. The course of the disease is more slowly progressive than that of chronic myeloid leukaemia, but death usually occurs within five years of the time of diagnosis. In elderly patients it tends to progress very slowly and may not materially shorten the expectation of life. An increase in the number of lymphoblasts is a grave prognostic sign as it frequently heralds an acute terminal phase.

The Malignant Lymphomas

(THE RETICULOSES)

These terms are applied to a group of neoplastic disorders affecting the reticulo-endothelial tissues and causing lymph node and splenic enlargement without the peripheral blood picture of leukaemia. The progressive proliferation of cells, which may initially start as a localised process, eventually becomes widespread and involves the bone marrow with replacement of normal haematopoiesis. Anaemia and suppression of normal immunity mechanisms occur in the more advanced stages of the disorders. Complex pathological classifications of these diseases are based on the type of reticulo-endothelial cell or cells that are responsible for the histological abnormalities seen in biopsies obtained from affected lymph nodes and the diagnosis is established in this way. Lymphosarcoma, reticulum cell sarcoma, giant follicular lymphoma and lymphadenoma (Hodgkin's disease), are included in the malignant lymphomas, the last named being the most common and important member of the group.

Lymphadenoma (Hodgkin's Disease)

This disease is characterised by progressive painless enlargement of lymphoid tissue throughout the body, and anaemia.

Aetiology. The disease occurs in both sexes, chiefly in adolescence and early adult life. The pathogenesis is unknown and the condition is regarded as a form of malignant disease allied to other tumours of the reticulo-endothelial system.

Pathology. Microscopic examination of the enlarged discrete lymph nodes shows a replacement of the normal structure by proliferation of reticulo-endothelial cells. Giant cells with two or three nuclei are seen, and there may be many eosinophils. The fibrous stroma is often increased. Caseation and necrosis are not found. Infiltration with greyish areas of Hodgkin's tissue causes enlargement of the spleen and liver. The bone marrow, lungs, kidneys and alimentary tract are also frequently involved though deposits are very rare in the nervous system. The type of histological picture gives an important indication of the degree of malignancy of the disease process in relation to treatment and prognosis.

Clinical Features. The disease has an insidious onset, enlargement of one group of superficial nodes usually occurring first. The cervical groups are often involved earliest. The progressive enlargement includes the axillary and inguinal groups and extends to thoracic and abdominal nodes which are occasionally affected first. The nodes are usually painless, discrete and rubbery, and they vary in size from about 2 to 6 centimetres in diameter. The skin is freely mobile over them. Pressure by the node masses and Hodgkin's deposits on neighbouring structures may cause a variety of features such as dysphagia, dyspnoea, venous obstruction, jaundice and paraplegia. The spleen is enlarged and usually palpable;

it is firm and painless, and its enlargement may be the earliest presenting feature. Enlargement of the liver is commonly present.

General features include progressive weakness and loss of weight. Fever is often present, and in some cases is of a low grade irregular type, while in others there are recurrent bouts of pyrexia with the temperature rising to 39° C. for several days, alternating with apyrexial periods (Pel-Ebstein fever). Fever is common in cases in which the spleen and abdominal lymph nodes are primarily affected. In many cases there is no fever until the terminal stages. Pruritus is a troublesome symptom in about 10 per cent of cases.

Anaemia is usual and progressive. It is commonly normochromic and normocytic and occasionally symptomatic haemolytic anaemia is present. There is no diagnostic change in the white cells. The count may be normal, but it is often moderately increased initially and decreased in the terminal phases when there is frequently accompanying thrombocytopenia. The proportion of granulocytes is usually increased, and 15 to 20 per cent of cases show a moderate eosinophilia. An important diagnostic point is that a lymphocytosis does not occur. Usually marrow puncture fails to reveal any diagnostic features, although occasionally and quite fortuitously the needle may penetrate a mass of Hodgkin's tissue in the sternal cavity.

Diagnosis. This involves the differential diagnosis of conditions producing enlargement of lymph nodes and of the spleen. The diseases with which Hodgkin's disease are most readily confused are: (1 *tuberculous lymphadenitis*, which is usually confined to the neck, in which the nodes may become matted together, may show caseation and sinus formation, and there is no splenomegaly; *chronic* (2 *pyogenic lymphadenitis* (chiefly also of the neck), in which the nodes are small and tender, a source of infection can be found, and there is no splenomegaly; (3 *lymphatic leukaemia*, in which the examination of the blood and bone marrow reveals the characteristic changes; (4 *infectious mononucleosis*, in which the lymph node and splenic enlargement is transient and the blood examination and a positive Paul-Bunnell test are diagnostic; *lymphosarcoma and reticulum cell sarcoma*, which can be distinguished only by microscopic examination of an excised node; *secondary syphilis* with generalised lymph node enlargement, in which the swelling is transient, a skin rash is common and serological reactions are positive; *the anaemia associated with portal hypertension* in which there is splenomegaly but lymph node enlargement is absent.

The diagnosis can be established with certainty only by biopsy of a lymph node. Liver biopsy may provide the diagnosis in cases with hepatic enlargement.

Treatment. Considerable advances have been made in the treatment of this disease with increasing hopes that cure may be achieved in some cases. Clinical classification into four stages according to the degree of involvement at the time of diagnosis is considered in relation to the histological changes shown at lymph node biopsy. The radiological technique of lymphangiography is used to determine the extent of lymph node involvement. In the most favourable cases where the disease is found to be limited to one anatomical site and unaccompanied by systemic symptoms (Stage 1), megavoltage irradiation yields most encouraging results with survival in good health for 10 years or more in about 50 per cent of patients. Even though the spleen is not enlarged in the early stages, splenectomy is now advocated in some centres as part of the initial treatment as histological examination has shown that early changes of the Hodgkin's process may be removed by this procedure.

In cases where the disease is found to be more widespread at the time of diagnosis more extensive radiotherapy is employed and courses of chemotherapy are used in addition. The latter become the mainstay of treatment in the more advanced stages of the disorder when the systemic effects and increasing anaemia render palliative therapy more difficult. As in the acute leukaemias the current trend in chemotherapy is to use courses of combinations of drugs which are more effective than agents used singly. A quadruple therapy course which has produced better remissions in Hodgkin's disease than those previously achieved combines prednisolone with mustine hydrochloride, procarbazine and vinblastine. Again as with the leukaemias the best results are obtained in centres with experience in dealing with such treatment.

Prognosis. The disease is fatal but in many cases is only slowly progressive. The five-year survival rate in patients with localised disease treated by radiotherapy exceeds 70 per cent, and it is not uncommon for such cases to enjoy good health for 10 to 20 years. When the disease is widespread the course is fairly rapid over a period of months. Histological features are also helpful in assessing prognosis.

Myelomatosis

This relatively uncommon malignant condition is associated with a neoplastic proliferation of abnormal plasma cells in the bone marrow. Myelomatosis is one of a group of disorders to which the name *paraproteinaemias* is given. They are characterised by an abnormal pattern of globulins in the peripheral blood believed to be produced by abnormal cells in the bone marrow (p. 28) and seen as a 'myeloma band' on electrophoresis. Certain of these conditions show an increase in the serum content of immunoglobulin M, and the term 'macroglobulinaemia' is then used. The plasma cells produce local tumours of bone, sometimes solitary at first, but eventually becoming widespread and in this form the condition is known as multiple myeloma.

Clinical Features. Myelomatosis occurs in either sex, chiefly after the age of 50 years. A common presenting symptom is back pain due to pressure on spinal nerve roots, and pathological fracture may occur in any bone involved. Vertebral body collapse may give rise to paraplegia. Increasing plasma cell replacement of the marrow is associated with progressive normocytic anaemia, and eventually there is also granulopenia and thrombocytopenia. In the variety known as diffuse myelomatosis the clinical picture is that of progressive marrow involvement without the formation of bony lesions, and, in the rare extramedullary type, soft tissue tumours may occur. There is usually no enlargement of the spleen, lymph nodes or liver. Other features are an undue liability to infections, especially of the respiratory tract, a very rapid ESR and Bence-Jones protein in the urine (p. 28). Precipitation of this protein in the tubules may cause renal failure but this may also result from the amyloidosis commonly associated with the later stages of myelomatosis. Hypercalcaemia is commonly present. The disease is fatal, usually in two to three years.

Diagnosis. This is based on bone marrow examination which reveals large numbers of plasma cells with a slate-blue cytoplasm and an eccentric, sometimes double, nucleus. Radiological examination of the skeleton may show widespread punched-out osteolytic areas best seen in the skull, ribs, pelvis and vertebrae, and diffuse osteoporotic changes are common. Determination of the electrophoretic pattern of the serum proteins is important and abnormal protein may be demonstrated in the urine.

Treatment. There is no curative treatment but localised irradiation will reduce the severity of bone pain and allow healing of spontaneous fractures. Courses of combined chemotherapy using large doses of prednisolone along with the alkylating agent melphalan repeated at regular intervals have achieved remissions of two years or more in cases treated in experienced centres. In cases with anaemia associated with marrow replacement, repeated blood transfusions may prolong life and intercurrent infections should be promptly treated. In the cases with renal failure, with high levels of serum uric acid or calcium, corticosteroid therapy is indicated.

Diseases of Lipoid Storage

GAUCHER'S DISEASE AND NIEMANN-PICK'S DISEASE

These are very rare familial disorders occurring most frequently in children of the Jewish race. They result from an enzyme deficiency and are characterised by the abnormal storage of lipoids in the cells of the reticulo-endothelial system, with consequent anaemia and splenomegaly. The conditions are slowly progressive and eventually fatal. There is no specific treatment available.

Hypersplenism

This term is used to describe the depression of leucocyte and platelet counts in the peripheral blood which is often encountered in a wide variety of conditions in which splenomegaly is a prominent feature, such as portal hypertension (p. 558). The cause of the leucopenia and the thrombocytopenia is not fully understood but it may in part be due to sequestration of leucocytes and platelets in the enlarged spleen.

HAEMORRHAGIC DISORDERS

Under this heading are included a large number of conditions characterised by an abnormal tendency to bleeding.

The factors concerned in the arrest of haemorrhage are many. They include (*a*) contraction of damaged small vessels, (*b*) the plugging of tears in such vessels by the aggregation of platelets, and (*c*) the coagulation of the blood which is believed to involve a chain of reactions between at least ten factors.

A. *The Vascular Factor*

Active contraction of capillaries in response to injury constitutes an essential feature of natural haemostasis. This, together with plugging of the bleeding points by platelets, gives time for clotting to occur before the injured vessels reopen.

B. *The Thrombocyte*

An adequate supply of normal platelets is of great importance in arresting haemorrhage. Not only do platelets take an important part in the production of thromboplastin, but they also play a mechanical role in the plugging of bleeding points in vessels. It is also possible that they may play some part in maintaining a normal resistance of capillary endothelium to injury. Even in thrombocytopenic states there are sufficient thrombocytes to initiate clotting.

C. *Intrinsic Factors concerned with the Coagulation of Blood*

Much of our knowledge of blood coagulation is hypothetical, but it may be said that when blood comes in contact with a foreign surface, an interaction is initiated which involves the platelets and a number of factors present in normal blood, including factors V, VII, VIII (antihaemophilic factor), IX (Christmas factor) and X. These interact in the presence of calcium ions to form thromboplastin, which activates prothrombin to thrombin. Prothrombin, which is produced in the liver, requires vitamin K for its synthesis. The thrombin produced reacts in turn with fibrinogen to form fibrin. The mechanism of interaction of clotting factors is a matter of great complexity, but the following scheme forms a basis for any discussion:

$$\left.\begin{array}{l}\text{Platelets}\\ \text{Factor V}\\ \text{Factor VIII}\\ \text{Factor IX}\\ \text{Factor X}\\ \text{Calcium ions}\end{array}\right\}\xrightarrow{\text{Factor VII}}\text{Thromboplastin.}$$

$$\text{Prothrombin}\xrightarrow{\text{Thromboplastin}}\text{Thrombin.}$$

$$\text{Fibrinogen}\xrightarrow{\text{Thrombin}}\text{Fibrin.}$$

Within the meshwork of the fibrin clot, red and white cells and platelets are enclosed. The fibrin filaments contract, the clot shrinks and becomes firmer and serum is expressed.

There is also a fibrinolytic mechanism which limits fibrin deposition by dissolving this protein. Plasminogen activator is released from damaged tissues and leads to the production of an enzyme, plasmin, from the inactive precursor, plasminogen, in the blood thus:

$$\text{Plasminogen} \xrightarrow{\text{Plasminogen activator}} \text{Plasmin.}$$

$$\text{Fibrin} \xrightarrow{\text{Plasmin}} \text{Fibrin degradation products.}$$

Classification of Haemorrhagic Disorders

The following classification is provisional, since in many forms the exact pathogenesis is not fully understood.

A. Due to Defects of the Capillary Endothelium

1. The vascular purpuras.
    - (*a*) Infections, e.g. typhus, typhoid, meningococcal meningitis, measles, infective endocarditis, septicaemia, smallpox.
    - (*b*) Chemical agents, e.g. aspirin, ergot, frusemide, indomethacin, iodides, phenobarbitone, phenylbutazone, phenytoin, quinine and snake venom.
    - (*c*) Anaphylactoid purpura.
    - (*d*) Senile purpura.
    - (*e*) Resulting from corticosteroid therapy and in Cushing's disease (p. 656).
    - (*f*) Metabolic purpura (uraemia, p. 597; hepatic failure, p. 560).
    - (*g*) Scurvy (p. 149).
2. Von Willebrand's disease.
3. Hereditary haemorrhagic telangiectasia.

B. Due to Deficiency of Blood Platelets

1. Idiopathic thrombocytopenic purpura.
2. Secondary or symptomatic thrombocytopenic purpura.

C. Due to Defects in the Clotting Mechanism

1. Haemophilia.
2. Christmas disease.
3. Hypoprothrombinaemia.
4. Congenital or acquired fibrinogenopenia.

The Diagnosis of Haemorrhagic Disorders

History. The guiding factors in the assessment of a patient with a haemorrhagic disorder include a knowledge of the sex of the patient, of any history of exposure to drugs or chemicals and of any recent infection. Enquiry should also be made about the family history and about the patient's response in the past to traumatic procedures such as tooth extraction or tonsillectomy.

Clinical Features. Purpura, which is not itself a disease but a manifestation of disease, is defined as bleeding into the skin or mucous membranes. The haemorrhagic spots do not disappear on pressure. Tiny purpuric haemorrhages about the size of a pinhead are known as petechiae. They are usually most prominent in the legs of the ambulant patient because of the increased hypostatic pressure, but even here they may be overlooked if inspection is cursory. Petechiae indicate a deficiency of platelets or a defect of the endothelium. Large purpuric haemorrhages are known as ecchymoses and these may be due not only to platelet or vascular deficiencies but also to coagulation defects. Bleeding into a joint (haemarthrosis) usually indicates a severe coagulation defect such as haemophilia. Bruising is not necessarily an indication of a haemorrhagic disorder as it may readily be induced in many healthy persons, particularly women.

Investigation. The decision about which tests to carry out and the order in which they should be performed depends upon the initial clinical appraisal. A platelet count is usually required but a rough indication of whether gross platelet deficiency exists can be obtained by examination of a blood film stained with cresyl blue. The bleeding time is prolonged in thrombocytopenia and is most reliably estimated by Ivy's method. In the assessment of coagulation defects the blood clotting time is an insensitive measure and is abnormally prolonged only when the coagulation factors are seriously deficient. More specific tests include the one stage 'prothrombin' time (p. 765), and estimations of the quantity of fibrinogen and thromboplastin. A useful rapid qualitative test for fibrinogen deficiency is readily available, whereas laboratory facilities are required for a test such as the partial thromboplastin time which detects coagulation defects too small to lead to prolongation of the whole blood clotting time. Many disorders of coagulation require specialised laboratory investigation.

A. Haemorrhagic Disorders due to Defects of Capillary Endothelium

The Vascular Purpuras

In this group of haemorrhagic diseases the lesion usually consists of damage to the capillary walls from the factors noted on page 758. In the types due to infections and chemical agents and in anaphylactoid purpura it is unusual to find qualitative or quantitative changes in the platelets and under these conditions the term non-thrombocytopenic purpura may be used. In a minority of cases of vascular purpura, however, the capillary damage is accompanied by a reduction in the number of platelets, due presumably to the combined effects of the toxic and sensitising factors mentioned above.

Anaphylactoid Purpura. The various clinical forms of this rare condition are manifestations of an allergic reaction but the antigen is often unknown.

Purpura Simplex is found in association with sensitivity to certain bacterial infections, notably streptococcal. Thus it occurs in rheumatic fever, scarlet fever, etc. Small haemorrhagic spots appear on the limbs or over the whole body. The condition is usually of no significance and calls for no treatment.

Henoch-Schönlein Purpura occurs in children and adolescents. Sero-haemorrhagic effusion into the wall of the gut may cause colic and melaena and intussusception may be simulated. Periarticular effusion may cause painful swelling of the joints. Mild fever is usual. Purpura of the skin may or may not be present. The prognosis is good but relapses often occur.

In anaphylactoid purpura other allergic manifestations are sometimes found in addition, such as urticaria or angioneurotic oedema. Acute nephritis is the most dangerous complication when the purpura is secondary to streptococcal infection. The platelet count and the bleeding and coagulation times are all normal. The capillary resistance test may be positive. The diagnosis may present great difficulty if purpura of the skin or mucous membranes is not present.

Senile Purpura. This is a benign condition found in elderly people, and related to atrophic changes in the skin which permit rupture of small vessels by shearing strains. Such haemorrhages are common on the dorsum of the hand and are slowly reabsorbed without a bruise.

MEASURES FOR CONTROL OF BLEEDING IN THE VASCULAR PURPURAS

The measures described for this purpose in the treatment of haemophilia (p. 763) are applicable in purpura except that transfusions must be of fresh whole blood.

In the treatment of purpura associated with infections, antibiotics may be of value. In the anaphylactoid group improvement sometimes occurs as a result of the administration of antihistamine drugs, or of corticosteroids in the dosage recommended for idiopathic thrombocytopenic purpura (p. 761). When purpura is a manifestation of scurvy, ascorbic acid should be given. Splenectomy is of value only in idiopathic thrombocytopenic purpura.

Von Willebrand's Disease

This rare disease that affects both sexes is inherited as a simple Mendelian dominant. The main defect is believed to be an abnormality of the capillaries. The bleeding time is prolonged but the coagulation time and platelet count are normal. In some cases a deficiency of antihaemophilic factor has been demonstrated. The bleeding manifestations include prolonged bleeding from minor injuries and tooth extractions, menorrhagia and haemorrhage from the gastrointestinal tract. Treatment is symptomatic, namely iron and blood transfusions as required. Splenectomy is contraindicated.

Hereditary Haemorrhagic Telangiectasia

This is a rare hereditary disease transmitted as an autosomal dominant trait (p. 7). It is characterised by bleeding from multiple telangiectases which consist of localised collections of non-contractile capillaries. It occurs in both sexes and the first and frequently the only symptom may be epistaxis. However haematemesis, haemoptysis or bleeding elsewhere may occur. Telangiectases are not usually prominent till the age of 20 or more and may be found on the face or hands, or in the mucous membrane of the nose or mouth. Treatment of bleeding areas is sometimes difficult, but cauterisation of the nose may be helpful.

B. Haemorrhagic Disorders due to Deficiency of Blood Platelets

Idiopathic Thrombocytopenic Purpura

This is a disease of unproved aetiology characterised by a quantitative deficiency of platelets; in some instances it may be due to an antigen-antibody reaction. The disease occurs most commonly in children and young adults. In children it frequently follows a viral infection.

Intermittent purpura and bleeding may occur in any site, most frequently from the nose, alimentary or urogenital tracts, and such bleeding may be fatal, especially should it occur in the brain or subarachnoid space. The disease is usually a chronic one with remissions and relapses, bleeding tending to occur when the platelet count falls below 40,000 per mm^3. The spleen is rarely palpably enlarged. The blood shows, in addition to the thrombocytopenia, a hypochromic microcytic anaemia, the degree depending on the amount of blood loss. The bleeding time is much prolonged, e.g. 15 to 20 minutes, and the capillary resistance test is strongly positive during relapse. The coagulation time is normal but the clot formed is soft, friable and retracts poorly.

Treatment. The effects of repeated transfusion of blood and large amounts of prednisolone (60 mg daily) should always be tried before surgery is contemplated. In a high proportion of cases remissions varying in degree and duration can be produced. In the majority of patients, however, cessation of corticosteroid therapy or reduction of dosage to a level which can be tolerated by the patient is usually followed by clinical and haematological relapse. If the bleeding tendency is not controlled or greatly improved by blood transfusion and corticosteroids within two weeks, splenectomy should be carried out without further delay. Within a few minutes of the removal of the spleen, the prolonged bleeding time and increased capillary fragility start to improve, to be followed within 24 to 48 hours by a rise in thrombocytes. Although these beneficial haematological effects are not always maintained, at least 80 per cent of cases of idiopathic thrombocytopenic purpura are greatly benefited by splenectomy. In children recovery usually occurs spontaneously or may follow corticosteroid therapy.

Secondary or Symptomatic Thrombocytopenic Purpura

Secondary or symptomatic thrombocytopenic purpura occurs in pancytopenia, leukaemia, hypersplenism, multiple neoplastic deposits in the bone marrow, from excessive exposure to X-rays or radioactive substances, and occasionally in very severe fevers. It may be found in megaloblastic anaemia and in systemic lupus erythematosus. It can follow massive blood transfusion.

Thrombocytopenia may be part of a general pancytopenia following drugs (p. 734). In addition patients may develop thrombocytopenia because of sensitivity to other drugs such as chlordiazepoxide, chlorothiazide, chlorpropamide, frusemide, indomethacin, oxyphenbutazone, certain sulphonamides and tolbutamide. Here the prognosis is much better, provided the drug is withdrawn and transfusion given as required. Platelet concentrates are available in some centres.

C. Haemorrhagic Disorders due to Defects in the Clotting Mechanism

Haemophilia (Factor VIII Deficiency)

Of the various factors in normal plasma concerned with the clotting mechanism, the most important from a clinical point of view is the antihaemophilic factor (Factor VIII, AHF or AHG), a deficiency of which leads to haemophilia. This factor is normally present in the globulin fraction of plasma.

Haemophilia is a hereditary disorder of blood coagulation characterised by a lifelong tendency to excessive haemorrhage and a greatly prolonged coagulation time. The haemophilia gene is transmitted as a sex-linked recessive character being carried on one of the X chromosomes. It therefore follows that the sons of a haemophiliac do not suffer from haemophilia and do not transmit the trait to their descendants. The daughters of a haemophilic man all carry the trait. Some of the sons of a female carrier suffer from haemophilia. Some of the daughters of a female carrier carry the trait. There is no method of detecting whether any woman of a haemophilic family can marry with impunity. In many instances no family history can be obtained.

Clinical Features. The bleeding tendency is not apparent at birth, but is usually noticed within the first three years. Haemorrhage occurs from the nose, in the mouth or alimentary tract, from the urinary tract, from injuries to the skin, into the muscles, subcutaneous tissue or joints, or after eruption or extraction of teeth, circumcision, tonsillectomy, etc. Some trauma is necessary for the initiation of the bleeding, but often this may be so slight as to pass unnoticed. Injury may in fact cause haemorrhage in any organ, including the brain and spinal cord. The characteristic feature of the bleeding is not its profuseness but its persistence, and the total loss of blood may be very serious. In nearly every case bleeding occurs at some stage into joints, most commonly the knees, ankles and elbows. When this happens there is pain and swelling o the joints, and fever. There can be repeated haemorrhages into joints without serious after-effects, but organisation of the blood clot may lead to firm ankylosis with marked deformity and crippling.

The coagulation time is usually prolonged and the bleeding time, platelet count and prothrombin time are normal. Anaemia may be a feature depending upon the extent of the bleeding.

Diagnosis. The occurrence of habitual haemorrhage in a male with a family history of bleeding in male relatives or forebears and with the haematological findings described above suggests that the diagnosis is either haemophilia or Christmas disease (p. 764). Occasionally, however, the coagulation time is normal. Such cases can now be recognised by certain but complex laboratory tests, one of the most useful of which is the thromboplastin generation test. Methods are being devised to detect the carrier state in females. There are haemophilia centres in all regions of Britain at which these investigations can be done. The patient is then issued with a card giving necessary information, including the diagnosis and blood group.

Treatment. Even for the most trivial surgical intervention, such as the extraction of a tooth, the patient must be given intravenously, before and after operation, fresh plasma or plasma that has been dried or frozen when fresh, or a special preparation of the globulin fraction of human plasma containing the antihaemophilic factor. Fresh blood is required to replace blood that has been lost. The management of the case requires careful planning by the dentist or surgeon, the physician and the blood transfusion officer.

When bleeding occurs the patient should be confined to bed. It may be necessary to give many pints of fresh plasma or blood over a period of several days. The administration of antihaemophilic factor also requires to be repeated intravenously at intervals of 24 hours or less, and this is the treatment of choice. The most widely used form is cryoprecipitate which is prepared in a two plastic bag system by collecting blood, centrifuging, transferring the plasma to the secondary pack, freezing it, and thawing at 40° C. At a few transfusion centres suitable concentrates are produced by other methods and superconcentrates are being developed. These must be Australia antigen negative. Antihaemophilic factor from bovine or porcine sources is available commercially. It is, however, antigenic and will cause sensitivity reactions which may be fatal if it is given for more than one short course of treatment. Hence it should be reserved for use in grave emergencies such as major operations. The post-haemorrhagic anaemia should be treated with iron.

Local measures consist of the application to the bleeding point (after cleaning away blood and clot) of dressings soaked in substances designed to promote haemostasis. These include Russell's viper venom, adrenaline, fresh whole blood, and preparations of thrombin. Soluble dressings such as gelatin sponge, oxidised cellulose or fibrin foam are useful. Epistaxis may require firm packing of the nose with gauze dressings. Bleeding from tooth sockets can be controlled by packs which may be retained in position by a special dental plate. It may be necessary to give an antibiotic because of the danger of infection, particularly in the mouth, but intramuscular injections should be avoided because of the danger of haematoma formation.

A joint which is the site of bleeding should never be opened surgically but should be splinted, lightly bandaged and protected. The same applies to haematomas. Aspiration should be avoided. Most patients obtain relief from the pain due to haemorrhage into a joint if cold packs or icebags are applied. Splinting of the limb should not be continued too long or fibrous ankylosis will result. Analgesics may be required but pethidine and morphine should be avoided because of the danger of addiction and aspirin should not be given in case it leads to a haematemesis.

Prognosis. In some patients the disease is mild, causing little inconvenience. In others it may be very severe, with recurrent joint haemorrhages and troublesome bleeding from minor cuts or after surgical procedures. The whole life of the haemophiliac is coloured by the fear of haemorrhage, particularly into the joints. With modern methods of treatment, the prognosis has improved greatly.

Prophylaxis. Since there is no known cure for the disease, haemophilic men, their sisters and their daughters should be strongly advised not to have children. Sterilisation should be considered. Limitation of the risks of bleeding involves the haemophiliac leading a sheltered and careful life with avoidance of trauma, but sufferers from the condition should not be encouraged to consider themselves as curiosities. Some children with mild haemophilia can attend ordinary schools, but for others education should be provided by the local authority either in the patients' homes or in a school for handicapped children. When the boy reaches the age of 14 or 15 the local Youth Employment Officer should be approached to assist in the choice of a career. Regular dental supervision is necessary as a prophylaxis against tooth extraction.

Christmas Disease (Factor IX Deficiency)

About one-tenth of the patients with the clinical picture of haemophilia can be shown by special laboratory tests, particularly the thromboplastin generation test, not to have haemophilia but Christmas disease, so-called after the surname of the first patient investigated in Britain. The condition is frequently less severe than haemophilia. The blood of these patients is not deficient in antihaemophilic factor, but in a different factor, the so-called Christmas factor, which is less labile than the antihaemophilic factor. Local and general treatment is the same as in haemophilia, except that preparations of antihaemophilic factor are of no value in the treatment of Christmas disease. At a very few centres, factor IX concentrates are available. Fresh frozen plasma is more commonly used.

Hypoprothrombinaemia

This condition is characterised by a deficiency of plasma prothrombin, a tendency to spontaneous and traumatic internal and external haemorrhage, and a prolonged coagulation time.

Prothrombin is formed in the liver from the fat-soluble vitamin K, which is ingested in certain foodstuffs (p. 148) and is also synthesised in the gut by bacterial action. The absorption of vitamin K from the intestine requires the presence of bile salts.

Hypoprothrombinaemia occurs:

1. In *haemorrhagic disease of the newborn*, which appears in about 1 in 800 births. The bleeding tendency is due to an exaggeration of the normal hypo-

prothrombinaemia which occurs 24 to 72 hours after birth. During this time there is no bacterial formation of vitamin K in the gut. Two to four days after birth, bleeding may occur into the alimentary tract (melaena neonatorum), into the skin or subcutaneous tissue, brain, spinal cord, peritoneal cavity, etc. In some cases so-called birth injuries may be due to bleeding consequent on hypoprothrombinaemia. Spontaneous recovery usually occurs in mild cases, but death may result in severe cases.

In the newborn, especially if premature, water soluble analogues of vitamin K may cause hyperbilirubinaemia and kernicterus (p. 879). Phytomenadione (vitamin K_1) is relatively free from these effects and can be given to the affected baby in a dose of 1 mg intramuscularly. Blood transfusion may also be required.

2. In *gross hepatic disease* bleeding results from impaired synthesis of prothrombin by the liver.

3. In *obstructive jaundice* there is a failure in absorption of vitamin K because of lack of bile salts.

4. In certain *diarrhoeal diseases* such as idiopathic steatorrhoea, fistulae and Crohn's disease there is a failure of absorption of vitamin K.

5. As a result of the administration of *warfarin* or *phenindione*. These anticoagulants are widely employed in the management of venous thrombosis and pulmonary embolism.

Dosage of anticoagulants is controlled by the test commonly referred to as the *one stage prothrombin time*. This is the time taken for plasma to clot under certain standard conditions, but it is a measure of the level, not only of prothrombin but also of certain other factors. Another test, the *thrombotest*, measures in addition factors IX and possibly X which may also be affected by these anticoagulants. Bleeding can result from factor IX deficiency when the result of the prothrombin time tests suggests that the dosage of warfarin or phenindione is satisfactory.

Treatment consists of the stoppage of the anticoagulant drug, the administration of vitamin K_1, 10 mg by mouth or by intravenous injection, and, occasionally the transfusion of fresh blood, especially if the bleeding has made the patient anaemic.

Congenital or Acquired Fibrinogenopenia

A deficiency of plasma fibrinogen, which may be complete or partial, may arise very rarely as a congenital abnormality or as a result of severe liver disease. Most often the condition occurs in the late stages of pregnancy with complications, and is believed to be due to the entry into the blood of thromboplastic substances derived from the placenta. The condition is recognised by the occurrence of a haemorrhagic tendency with a prolonged coagulation time. The congenital form is distinguished from haemophilia by its occurrence in both sexes, the absence of a family history, and by the chemical determination of the amount of fibrinogen in the blood.

Blood transfusion may be required for the anaemia, but for the treatment of fibrinogenopenia the giving of concentrated plasma or of a preparation of the fibrinogen fraction of blood is essential. The clotting abnormalities may be complex, and expert assistance should be sought.

Thrombocytosis

An increased number of platelets may be found

(*a*) after haemorrhage and, to a lesser extent, after operation or injury;
(*b*) after splenectomy;
(*c*) in myeloproliferative disorders:
    (i) in chronic myeloid leukaemia;
    (ii) in some cases of polycythaemia vera and of myelofibrosis;
    (iii) in a rare primary disease called haemorrhagic thrombocythaemia with excessive production of abnormal platelets.

PREVENTION OF DISORDERS OF THE BLOOD

The most common blood disorder both in Britain and in other countries is chronic nutritional hypochromic anaemia in women of the child-bearing age. The essential cause of this anaemia is that the dietary intake of iron is insufficient to meet the physiological requirements. The regular consumption of a well-balanced diet containing foods rich in iron, such as liver, meat, peas, lentils, beans and green vegetables, will accomplish much in the prevention of this disorder. In addition, during pregnancy and lactation, when menstruation is heavy, and when malabsorption may follow operations on the stomach and small intestine, prophylactic administration of oral iron is indicated. It is important to make sure that sites of chronic blood loss, such as alimentary bleeding, are investigated and dealt with where possible. In countries where hookworm infection is rife, this is essential.

Attention has also been drawn to the frequency of nutritional hypochromic anaemia in infancy and childhood. Prophylactic iron should be given to infants of low birth weight and to those recovering from infections. The institution of a good mixed diet by the fourth month is also of importance in this respect.

The megaloblastic anaemias in general are not susceptible to prevention with the exception of types due to direct dietary deficiency, most commonly encountered in the tropics and in pregnancy (p. 731). The prevention of subacute combined degeneration of the spinal cord in Addisonian pernicious anaemia by early diagnosis and efficient treatment cannot be too strongly emphasised. Expensive preparations containing iron and folic acid should not be used blindly in uninvestigated cases of anaemia. Treatment with hydroxocobalamin by injection will be necessary after total gastrectomy and the possibility of megaloblastic anaemia developing some years after partial gastrectomy or, even more rarely, gastroenterostomy, or from disease or resection of the ileum, should be borne in mind.

The aetiology of most of the other blood disorders is not known and hence prophylactic measures are not always possible. This is true of the idiopathic forms of haemolytic anaemia, pancytopenia, thrombocytopenic purpura and agranulocytosis. However, some types of these disorders may develop secondary to toxic or infective agents known to have deleterious effects on the bone marrow or circulating blood. Avoidance of such factors where possible, and careful observation of individuals exposed to these hazards are obvious precautions which must be carried out.

Blood transfusions may be responsible for the transmission of disease, e.g. serum hepatitis, malaria, and syphilis or for the production of severe reactions if the blood groups are incompatible. It is well recognised that women requiring blood transfusion must be given blood of the same Rh type as themselves, in order to avoid the production of antibodies liable to cause haemolytic reactions after subsequent transfusions or haemolytic anaemia in their future offspring. Accordingly a knowledge of the dangers associated with blood transfusions can lead to highly successful prophylactic measures for their avoidance. Measures to anticipate the development of haemolytic disease of the newborn are discussed on page 739.

In the prevention of haemorrhagic diseases mention need be made of haemophilia, Christmas disease and hypoprothrombinaemia. With regard to the former two disorders female carriers of the trait should be told that for the sake of posterity child-bearing should not be undertaken and sterilisation should be considered.

Hypoprothrombinaemia arising in obstructive jaundice, biliary fistulae, chronic diarrhoeal diseases such as idiopathic steatorrhoea, and in some newborn infants can be prevented and corrected by the parenteral administration of vitamin K_1. Such prophylactic treatment may be the means of avoiding a severe or fatal haemorrhagic state.

The possibility that ionising radiation may be responsible for genetic changes leading to leukaemia must be borne in mind and all unessential irradiation, whether for diagnostic or therapeutic purposes, must be avoided.

R. H. GIRDWOOD.
JAMES INNES.

Further reading:

Alstead, S. & Girdwood, R. H. (1974). *Textbook of Medical Treatment*, 13th ed. Edinburgh and London: Churchill Livingstone.—For further information about treatment of blood disorders and the use of blood and blood products.

Dacie, J. V. & Lewis, S. M. (1970). *Practical Haematology*, 4th ed. Edinburgh and London: Churchill Livingstone.—For information regarding investigative procedures.

Thompson, R. B. (1969). *A Short Textbook of Haematology*, 3rd ed. London: Pitman.

Wintrobe, M. M. (1967). *Clinical Haematology*, 6th ed. London: Kimpton.

Wright, F. J. & Baird, J. P. (1971). *Tropical Diseases Supplement*, 4th ed. Edinburgh and London: Churchill Livingstone.—For an account of anaemia in the tropics.

Diseases of Connective Tissues, Joints and Bones

In recent years the miscellaneous group of conditions primarily involving the musculo-skeletal structures has been the subject of intense study. Much has been learned about their clinical features, course and prognosis. Diagnosis has been rendered more precise by an increasing number of serological and biochemical tests. A wide range of effective therapeutic measures has become available. Extensive study of the pathological changes has revealed that the primary lesion, whether inflammatory or degenerative in nature, involves the connective tissue matrix. The term, 'diseases of connective tissue' would therefore seem more appropriate for this group of conditions than the time honoured 'chronic rheumatic diseases'.

It is convenient to consider first those diseases in which symptoms arise as a result of diffuse inflammatory changes. These include rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, dermatomyositis, scleroderma, polyarteritis, polymyalgia rheumatica and gout.

Another large group consists of those disorders in which symptoms arise as a result of degenerative changes in connective tissue, and includes osteoarthrosis, intervertebral disc disease and a miscellaneous group of painful syndromes in which the joints themselves do not appear to be involved. There is also a small group of rare inherited disorders of connective tissue such as Marfan's syndrome (p. 303) and others in which the skin is particularly involved.

Diseases of connective tissue are responsible for much temporary or permanent disablement. In the year ended June 1967, just over one million spells of incapacity among the insured population in Britain were due to 'rheumatic complaints' and caused a loss of productivity of £190 million. Time lost from work amounted to 35·19 million days. 'Rheumatic complaints' were second only to accidents as regards the number of people affected and second only to bronchitis for the number of days lost.

Surveys in general practice suggest that nearly 10 per cent of the work of family doctors is devoted to the diagnosis and treatment of musculo-skeletal disorders grouped under the term 'rheumatism'.

Rheumatoid Arthritis

Rheumatoid arthritis can be defined as a chronic polyarthritis affecting mainly the more peripheral joints, running a prolonged course with exacerbations and remissions, and accompanied by a general systemic disturbance. The disease is characterised by swelling of the synovial membrane and periarticular tissues, subchondral osteoporosis, erosion of cartilage and bone and wasting of the associated muscles.

Aetiology

1. *Age.* The average age at onset is about 40, but the disease may occur at all ages. It is less common before puberty.

2. *Sex.* Females are affected two to three times as frequently as males.

3. *Heredity.* Although the influence of heredity is not known, a family history of the disease is not infrequently obtained.

4. *Climate.* In the past it was believed that the disease was most common in temperate zones and was particularly associated with cold and damp. Whilst the incidence is less in tropical countries a recent survey of the population of a subtropical region has shown that rheumatoid arthritis is as common there as in temperate climates, although it tends to be less severe.

5. *Infection.* It can be stated that rheumatoid arthritis is not due to invasion of the joints by any organism which can be demonstrated regularly by methods available at the present time although there is a growing body of opinion that a viable agent may be concerned in initiating the disease.

6. *Autoimmunity.* The presence in the serum of abnormal immunoglobulins in a high proportion of patients together with the histological appearances in the synovium and lymphoid tissue have led to the idea that rheumatoid arthritis may be associated with a derangement of the immune response to exogenous antigens or to antigens derived in part at least from the patient's own tissues. The characteristic immunological abnormality is the development of rheumatoid factor, usually IgM, which behaves primarily as an antibody to human IgG—i.e. as an autoantibody.

7. *Psychological Factors.* Rheumatoid arthritis is sometimes precipitated and often aggravated by emotional disturbances or excessive and long-continued worry and overwork.

In summary, the aetiology of the disease remains obscure, but it may well arise as a result of the interplay of a number of factors, some of which may be genetically determined while others may be of environmental origin.

Pathology. The earliest change is swelling and congestion of the synovial membrane and the overlying connective tissue, which become infiltrated with lymphocytes, plasma cells and macrophages. Effusion of synovial fluid into the joint space takes place during the active phase of the disease. Subsequently, hypertrophy of the synovial membrane occurs. Inflammatory granulation tissue or pannus is formed, which spreads over and under the articular cartilage with patchy destruction of the cartilage. Later, fibrous adhesions may form between the layers of pannus across the joint space and fibrous or even bony ankylosis may occur. Muscles adjacent to inflamed joints atrophy and there may be focal infiltration with lymphocytes.

Subcutaneous nodules have a characteristic histological appearance. There is a central area of fibrinoid material consisting of swollen and fragmented collagen fibres, fibrinous exudate and cellular debris, surrounded by a palisade of radially arranged proliferating mononuclear cells. The nodule is surrounded by a loose capsule of fibrous tissue. Similar granulomatous lesions may occur in the pleura, lung, pericardium and sclera. Lymph nodes are often hyperplastic and show many lymphoid follicles with large germinal centres. Plasma cells are numerous in the sinuses and medullary cords.

Clinical Features. In many cases the onset is insidious. For a period of weeks or months before the joints are clinically involved the patient may complain of transient articular or muscular pain and stiffness, tiredness, general malaise, fatigue, numbness and tingling in the extremities, loss of weight and vasomotor disturbances. In less than 10 per cent of cases the onset may be acute with fever and rapid involvement of many joints. Some patients may present with acute episodes of pain in various individual joints before developing polyarticular symptoms. In the typical case the small joints of the fingers and toes are the first to become affected. Swelling of the proximal interphalangeal joints gives rise to the typical spindled appearance of the fingers. As the disease progresses it spreads to involve such joints as the wrists, elbows, shoulders, ankles and knees. Only in more severe cases are the hips affected. The temporo-mandibular and sternoclavicular joints are occasionally involved. Muscular stiffness is a prominent symptom, and it is particularly marked in the morning or after periods of inactivity. As the disease advances, joint pain and swelling increase and muscular stiffness becomes more marked. Muscular atrophy takes place early and becomes a very prominent feature.

During the active stage of the disease signs of a systemic disturbance are present. Low-grade pyrexia, tachycardia, hypochromic normocytic anaemia, mild polymorph leucocytosis, raised erythrocyte sedimentation rate (ESR), altered plasma protein pattern (increased globulin and fibrinogen; decreased albumin) and lymphadenopathy are commonly found.

In more advanced cases pain and muscle spasm give rise to flexion deformities in the joints. At first these deformities are correctable, but later permanent contractures develop and the joints may become completely disorganised. The characteristic deformity in the hands is anterior subluxation of the metacarpophalangeal joints and ulnar deviation of the fingers.

In the early phase the disease is characterised by remissions and relapses. At this time radiological examination of the affected joints will show only demineralisation of the bone ends. Later, as the pathological process progresses to involve the articular cartilage, there is narrowing of the joint space and marginal erosions appear. In the late stages, in joints which are still capable of some movement, radiological examination will show the appearance of osteoarthrosis, which arises as a secondary manifestation in the damaged joints. In joints which have been immobilised by pain and muscular spasm, fibrous or bony ankylosis may take place. Subcutaneous nodules appear in 10 to 20 per cent of patients. The most common site is the extensor surface of the forearm just distal to the elbow joint. They may also occur over the patella, scapula, sacrum, scalp and along the tendons of the fingers and toes. In severe cases amyloidosis may complicate the later stages of the disease.

Diffuse vasculitis is a common feature of rheumatoid arthritis, especially in patients with nodules and a positive sensitised sheep cell test (p. 772). Leg ulcers, episcleritis, scleritis, keratoconjunctivitis sicca, pericarditis, pleurisy and peripheral neuropathy are among the extra-articular manifestations encountered in these circumstances.

Differential Diagnosis. In the average case of rheumatoid arthritis there is usually little difficulty in reaching a diagnosis, but when the disease starts in an atypical manner it will have to be distinguished from the following conditions:

1. *Rheumatic Fever*. In this condition the joint pain is of a flitting character.

The fever is usually higher and spindling of finger joints is rare. Occasionally subacute rheumatic fever may be difficult to distinguish from rheumatoid arthritis with a febrile onset, but the articular symptoms of rheumatic fever are more likely to be suppressed by full doses of aspirin. The ASO titre (p. 261) will usually be elevated in rheumatic fever.

2. *Gonococcal Arthritis.* An acute arthritis with fever may follow a gonorrhoeal infection, but since the advent of antibiotics this complication has become much less frequent. It can be distinguished from rheumatoid arthritis by a history of urethritis preceding the joint symptoms by two or three weeks. In the majority of cases demonstration of the gonococcus in smears from the urethra, prostate or cervix uteri will confirm the diagnosis. In only about 25 per cent, however, can the gonococcus be cultured from the synovial fluid but the gonococcal complement fixation test is usually positive.

3. *Reiter's Disease.* This disease is characterised by acute urethritis or diarrhoea, conjunctivitis and arthritis. The condition may occasionally be difficult to distinguish from rheumatoid arthritis when the syndrome is incomplete. The joint symptoms in Reiter's disease usually clear up completely on treatment with tetracycline. In a small proportion of cases the disease becomes chronic and involvement of the spine and sacro-iliac joints may develop. Characteristic skin lesions ('kerato-derma blennorrhagica') may be seen.

4. *Acute Pyogenic Arthritis.* This is usually monarticular. The joint is acutely inflamed and painful. The signs of a generalised infection, including high fever, are present. Both blood and synovial fluid should be cultured. Occasionally rheumatoid arthritis may be complicated by a super-added pyogenic arthritis which is almost invariably associated with a septicaemia and may be masked by corticosteroid therapy.

5. *Gout.* This arthritis in its earlier stages may be confused with the acute episodic variant of rheumatoid arthritis. In the classical case of gout the first joint to be affected is the metatarso-phalangeal joint of the big toe. The onset is very sudden, the pain extremely acute, but the attack usually responds dramatically to specific treatment (p. 785), leaving no residual changes in the joint. A high blood uric acid will usually be found in this disease.

6. *Tuberculous Arthritis.* The onset is insidious. Usually only one joint is involved, but occasionally several are affected. The condition is most common in children. In adults tuberculosis of the spine is the most common form. The radiological appearances, demonstration of the organisms in the synovial fluid or biopsy of the synovial membrane will differentiate this condition from rheumatoid arthritis.

7. *Osteoarthrosis.* This usually affects the larger joints such as the knees, hips and spine. In middle-aged women, however, osteoarthritic changes not uncommonly affect the fingers, and care should be taken to distinguish this condition from rheumatoid arthritis. In a typical case Heberden's nodes (p. 787) appear in relationship to the terminal interphalangeal joints. At first these nodes may be painful, but later they subside to leave a firm hard nodule which frequently causes deformity of the distal interphalangeal joint. The ESR is usually within normal limits.

8. *Psoriatic Arthritis.* It is now accepted that an erosive arthritis distinct from rheumatoid arthritis may complicate psoriasis. It is characterised by early

involvement of the terminal interphalangeal joints, ridging, thickening, cracking and pitting of the nails, and the absence of subcutaneous nodules. The spine and sacro-iliac joints are not infrequently affected.

9. *Brucellosis.* This condition may be suggested by a history of a possible source of infection or by an intermittent pyrexia and confirmed by a positive agglutination test (p. 78).

10. *Osteomyelitis.* Here pain and tenderness are maximal over the bone rather than the joints.

EXAMINATION OF SYNOVIAL FLUID. In cases of doubt this may provide valuable information. When infection is suspected fluid should be cultured and inoculated into guinea-pigs. In gout, uric acid crystals may be seen on microscopic examination. Fluid from traumatic or degenerative forms of arthritis is clear, viscid, does not clot and contains few cells. In rheumatoid arthritis or pyogenic infection the fluid is of low viscosity, turbid, clots on standing and contains many cells.

SENSITISED SHEEP CELL TEST. A serological test has become available which has proved valuable in the diagnosis of atypical forms of rheumatoid arthritis. It is known as the Rose-Waaler or sensitised sheep cell test and is positive in 65 to 70 per cent of cases of rheumatoid arthritis. It depends on the presence in the sera of rheumatoid factor; this immunoglobulin agglutinates sheep erythrocytes sensitised with anti-sheep cell antibody produced in the rabbit (p. 33). The test is also positive in 25 to 30 per cent of patients with systemic lupus erythematosus and in 15 to 20 per cent of cases of juvenile rheumatoid arthritis (Still's disease) but not in the other conditions discussed above. Latex particles coated with human IgG form the basis of a simplified and more sensitive but less specific serological test (latex fixation test).

Treatment. As the aetiology of the disease is unknown, treatment must be directed towards the relief of symptoms, the improvement of the patient's general health and the conservation and restoration of function in the joints damaged by the disease process. In achieving these objectives important measures are rest for the inflamed joints, physiotherapy, analgesics, anti-inflammatory agents, corticosteroids in selected cases, various surgical procedures and a co-ordinated rehabilitation programme.

1. GENERAL MEASURES IN THE ACUTE PHASE. When many joints are swollen and painful and when signs of severe constitutional disturbance. such as fever, anaemia and rapid ESR are present, the patient should be confined to bed until these signs and symptoms begin to subside. This period of general rest may last for several weeks and certain measures must be adopted to prevent unnecessary deterioration in physical efficiency. Attention should be directed to the maintenance of good posture. The mattress should be firm or fracture boards should be inserted beneath it. A firm back rest with the minimum number of pillows should be in position during the day; at night only one firm

head pillow should be allowed. A roomy cage with a padded footrest should be placed over the legs and feet; pillows behind knees should be forbidden; after the midday meal the patient should spend an hour resting flat with a small pillow under the lumbar spine. A further 15 minutes should be spent in the prone position with a pillow under the abdomen. Foot and quadriceps exercises should be performed daily by all patients confined to bed. The general level of physical efficiency should be maintained by the use of suitable exercises. These exercises are designed to have their effect on the groups of muscles in the thoracic, gluteal and abdominal regions. Rest in bed, by the cessation of weight-bearing on the inflamed joints, will go far towards fulfilling the first principle of treatment—the relief of symptoms, as pain and spasm are largely conditioned by movement and weight-bearing. Most patients in the acute phase of the disease will have lost weight and the diet should be of high caloric value with ample protein. Additional vitamin concentrates are not necessary if a well-balanced diet containing milk, eggs and fruit is eaten. A liberal supply of milk should be given to ensure an adequate intake of calcium and first-class protein.

2. LOCAL MEASURES IN THE ACUTE PHASE. Experience has shown that the correct treatment of the inflamed joints may be of fundamental importance in controlling both local and systemic symptoms in rheumatoid arthritis. Painful joints should be immobilised in skin-tight plaster of Paris splints. These splints should be maintained in position until the more acute symptoms have subsided. In the past undue emphasis may have been placed on the use of daily active and passive movements at this stage. The symptoms of inflammation subside more quickly if the joints are left at complete rest for a period of one to three weeks. The danger of joints becoming ankylosed if immobilised in this way has been exaggerated. The principle of a period of complete rest is of particular importance in the treatment of weight-bearing joints. When pain and swelling have subsided the splints are removed for active non-weight-bearing exercises. The patient should be taught these exercises and instructed to perform them frequently throughout the day. The application of heat before the sessions of exercise is useful in relieving stiffness. When the constitutional symptoms have begun to subside and power has been restored to wasted muscles, the patient is allowed up for increasing periods. Wax baths are beneficial in reducing stiffness in the joints of the hands and feet. Faradic foot baths may be helpful in initiating activity in the intrinsic muscles of the feet. Residual pain may be eased by radiant heat, infra-red rays or shortwave diathermy.

Occupational therapy is of considerable value in restoring manual dexterity and conditioning the patient for a return to productive employment.

3. ANTI-INFLAMMATORY AND ANALGESIC DRUGS. *Aspirin*, undoubtedly the most valuable anti-inflammatory agent for controlling symptoms, should be given to the limit of the patient's tolerance. The dose will range from 4 to 6 g daily. Aspirin soluble tablets (B.P.) is the preparation of choice. When pain is severe, tab. codeine. phos. (B.P.) 30 mg two to three times daily should be prescribed. Aspirin may cause gastrointestinal bleeding, but rarely in amounts greater than

2-6 ml daily. Dyspepsia may be troublesome, in which case enteric coated tablets should be prescribed. *Paracetamol* is less effective in controlling symptoms, but may be used when aspirin is poorly tolerated. The dose is 6-8 g daily. The long-term use of preparations containing phenacetin should be avoided as they can produce renal damage (p. 620).

Phenylbutazone is effective in controlling symptoms. The dose should not exceed 300 mg daily. Toxic effects occur in 20 to 40 per cent of patients. Most common are nausea, vomiting, rashes and oedema due to sodium retention. More serious complications in the form of haematemesis, perforation of peptic ulcers, agranulocytosis, thrombocytopenia, aplasia of the bone marrow, haematuria, anuria, chromosomal abnormalities and an increased incidence of leukaemia have been reported. An enteric coated preparation has been introduced which is claimed to reduce gastrointestinal intolerance. The drug should be used only when the response to aspirin and the conservative measures described has been unsatisfactory. It should not be prescribed if there is evidence of gastrointestinal, renal or cardiovascular disease.

Other anti-inflammatory drugs have been introduced in recent years. In general they are less effective but less toxic than phenylbutazone but may be tried when this drug or aspirin is ineffective or contraindicated. They include *mefenamic acid* (up to 600 mg daily), *flufenamic acid* (300-600 mg daily), *indomethacin* (up to 100 mg daily) and *ibuprofen* (600-800 mg daily). Mefenamic and flufenamic acid may cause gastrointestinal upset. The main side-effects of indomethacin are headache, vertigo, depression, nausea and vomiting. Rarely peptic ulceration and haemorrhage occur. Ibuprofen occasionally causes dyspepsia and, rarely, a rash. Recent multicentral trials of d-penicillamine (p. 877) indicate that this may be a useful drug in a dosage of 1·5 g daily.

If pain is severe, more potent analgesic drugs such as *dihydrocodeine* (30-60 mg) or *pentazocine* (25-100 mg) may be prescribed as required.

4. CORTICOSTEROIDS. The potent anti-inflammatory properties of corticosteroids are counterbalanced by their adverse effects, especially if used in high dosage on a long term basis. Their use can therefore be justified only if less potentially dangerous therapy is ineffective.

Prednisolone and Prednisone. Since Hench and his colleagues in 1948 first demonstrated the dramatic effects of cortisone in controlling the symptoms and signs of rheumatoid arthritis even more potent synthetic corticosteroids have been developed. Of these the most generally useful are still prednisolone, developed from hydrocortisone (cortisol) the natural hormone of the adrenal glands and prednisone, a modification of cortisone. The former is in more general use, optimum daily dose being 10 mg or less. For relieving disabling morning stiffness, 2·5-5 mg at bedtime is often effective. Major adverse effects are very likely to occur in patients receiving 20 mg or more daily. To reduce the incidence of dyspepsia and peptic ulceration the tablets should be crushed and taken along with food. Alternatively enteric-coated and soluble preparations are available which should be used in patients with dyspepsia or with a previous history of peptic ulceration.

Other Synthetic Corticosteroids. A number of other synthetic corticosteroids have been produced (p. 669). There is no evidence that they have any advantage over prednisone or prednisolone which are still the drugs of choice when corticosteroid therapy is indicated.

Adverse Effects. Corticosteroids should be used with great caution and only in patients who have failed to respond to an adequate trial of more conservative measures and in whom the disease is running a progressive downhill course. They should be used with particular care in patients with acute peptic ulceration, diabetes mellitus, hypertension, or osteoporosis. Infections will not be masked by moderate doses, but the additional stress of illness, injury or operation may make necessary a temporary increase in dosage (p. 667). All patients on corticosteroids should carry a card indicating the name of the preparation being used, its daily dose, and the address of the physician or hospital responsible for their supervision. Should withdrawal of corticosteroids become necessary, this must be done very slowly, the dose being reduced by not more than 2·5 mg weekly of prednisolone or prednisone.

Local Use of Corticosteroids. The intra-articular injection of a suspension of hydrocortisone acetate is followed by a reduction of pain and swelling. Duration of relief varies from a few days to two to three weeks in individual patients, but is worthwhile in over half the cases treated. The dose used varies from 5 mg in the small joints of the fingers to 50 mg in the case of the knee.

Repeated injections of corticosteroids at short intervals should be avoided, particularly in the case of weight-bearing joints, as rapid deterioration of the radiological appearances have been noted in the absence of a recurrence of symptoms.

Painful ligamentous attachments, tenosynovitis around the wrist and ankle, and nodules in tendons leading to limitation of movement can also be treated by local injection of hydrocortisone.

Eye drops of hydrocortisone (1·5 per cent solution) are valuable in controlling inflammatory conditions of the eye which occur not infrequently in the more severe cases of rheumatoid arthritis.

Corticotrophin (ACTH). Stimulation of the patient's own adrenal glands by the injection of corticotrophin is as effective as the administration of corticosteroids by mouth. Stable, long-acting preparations are available, which need only be injected once daily. Side-effects are similar to those which may complicate treatment with corticosteroids, but fluid retention and hypertension are more common. On the other hand, dyspepsia and peptic ulceration occur less frequently. The initial dose is 40 units daily. In most cases a satisfactory response is maintained by a dose of between 20 and 30 units daily. Patients can be taught to inject themselves. It is claimed by the advocates of this form of treatment that a remission of the disease occurs in a significant number of patients (15 of 78 patients in one report) which is maintained after the slow withdrawal of the hormone. In contrast, treatment can rarely be stopped in patients who have been on oral corticosteroids for any length of time. The disadvantage of daily injection and the development of resistance to the hormone limits the value of corticotrophin, but it may have a place in the treatment of severe and progressive cases who cannot tolerate corticosteroids.

Some of the disadvantages of corticotrophin have been overcome by the introduction of the hormone in synthetic form (tetracosactrin). This is available as a depot preparation and can be injected intramuscularly in a dose of 0·5-1 mg twice weekly.

5. GOLD SALTS. Evidence of the effectiveness of gold salts in some cases of rheumatoid arthritis has been provided by a controlled trial conducted under the auspices of the Arthritis and Rheumatism Council. A water-soluble preparation such as Myocrisin, a 50 per cent solution of sodium aurothiomalate, is recommended. Intramuscular injections of 50 mg are given at weekly intervals to a total of 1 g. If there is little or no response after the full course of injections, gold therapy should be discontinued. In other cases, improvement may be maintained by the continued administration of 50 mg every three or four weeks over a period of many months. Adverse reactions may occur at any time during treatment, dermatitis being the commonest. Thrombocytopenia, agranulocytosis and anaemia may result from depression of bone marrow. Only rarely has evidence of renal or hepatic damage been recorded.

The most important measure during the administration of gold salts is to impress on the patient the necessity of reporting immediately any untoward symptoms. Before each injection the patient should be asked specifically about pruritus or rash.

Treatment of Toxic Reactions. Dimercaprol combines with heavy metals to form a stable compound which is rapidly excreted in the urine. It is given by intramuscular injection in doses of 3 mg/kg body weight every six hours for three to four days. It should be used if signs of toxicity persist for more than a few days after injections of gold have been stopped. Should agranulocytosis develop, antibiotics should be given in full doses (p. 745). For more severe reactions prednisolone 15-20 mg daily has proved valuable in controlling symptoms.

6. CHLOROQUINE AND HYDROXYCHLOROQUINE. These anti-malarial drugs are moderately effective in rheumatoid arthritis and may be used as an adjunct to basic treatment. The dose of chloroquine phosphate is 250 mg daily and of hydroxychloroquine sulphate is 400 mg daily. Although these drugs are relatively toxic, they are more acceptable than corticosteroids for long-term use. Side-effects include rashes, gastrointestinal upsets, headaches, mental disturbance and leucopenia. Corneal deposits of the drug may produce disturbances of vision which disappear when the drug is withdrawn. More rarely, permanent visual impairment results from retinopathy. Ideally the eyes should be examined every three to six months during long-term therapy with these drugs.

7. IRON. The anaemia is notoriously resistant to iron given by mouth. Possibly iron may be deviated to local sites of inflammation. However, in the majority of cases improvement follows the administration of iron by intramuscular or intravenous injection (p. 726). A total of 2 g should be given in divided doses over a period of two weeks. Iron utilisation may be increased by adding ACTH 10-20 units daily during the course of iron injections.

8. TREATMENT OF MILD CASES. Many patients suffering from rheumatoid arthritis never become severely incapacitated, as the disease frequently runs a mild subacute course and can be kept under control with anti-inflammatory

ugs. These patients should be under periodic clinical observation. Physio- erapy and remedial exercises on an out-patient basis may do a great deal wards maintaining these patients at a good functional level. The measures tailed for the active stage should be started if symptoms become acute.

9. SURGICAL TREATMENT. Orthopaedic surgeons, particularly when working close collaboration with physicians, have important contributions to make to eatment. In rheumatoid arthritis involvement of extra-articular structures is sponsible for much of the disability, particularly in the earlier stages of the sease. Involvement of tendons and their synovial sheaths, at the wrists and the palm, the growth of nodules in the substance of tendons leading to upture, compression of the median nerve in the carpal tunnel, inflammation in ursae in relation to joints and contracture of joint capsules can also impair unction before significant damage has occurred within the joints. All can be ffectively dealt with surgically. At a later stage, when the synovial membrane as become inflamed and hypertrophied, synovectomy in both large and small oints can be followed by local remission of activity for prolonged periods. When cartilage and bone have been eroded and the mechanics of joints disturbed, rthroplasty, arthrodesis and the insertion of prostheses to replace damaged tructures play a valuable part in treatment. Pain in the forefoot, resulting rom clawing of the toes and callosities over the eroded heads of the metatarsal ones, can be completely relieved by excision of the heads and necks of all ive metatarsals, avoiding much wasteful expenditure on surgical shoes, which rarely control symptoms effectively.

There are many other situations where collaboration between surgeon and physician can be more effective than either working independently. When hips have been damaged to an extent that pain is incapacitating, total hip replacement by a number of techniques has been remarkably successful. This applies in rheumatoid arthritis, osteoarthrosis and ankylosing spondylitis. Work is progressing in the design of similar prostheses for other joints both large and small. It has now become essential for units dealing with all forms of arthritis to establish combined clinics with their surgical colleagues to reach decisions as to what should be done and when it should be done and to plan post-operative care and assessment in conjunction with physiotherapists, occupational therapists and social workers.

10. REHABILITATION. When the patient cannot return to a former occupation it will be necessary to suggest a change of employment where less strain will be thrown on the damaged joints. Training schemes are available in special centres in Britain. Rehabilitation and vocational training constitute an essential part of any scheme for the treatment of the chronic arthritic diseases. It cannot be emphasised too strongly that adequate treatment initiated in the early stages enables most patients to return to some form of wage-earning activity. Hopeless crippling can be prevented even in some of the 25 per cent of cases running a progressive course.

Prognosis. Rheumatoid arthritis usually runs a subacute or chronic course over a period of years. Its progress may be interrupted at any stage, so that no patient with rheumatoid arthritis should be considered as being beyond medical aid. In severe cases the disease progresses by a series of exacerbations and remissions. Each acute attack causes further damage to the joints, deformity and disability and the patient may become completely bedridden. Relapses may be precipitated by a variety of factors such as intercurrent infection, cold, damp, worry, overwork, or excessive use of the affected joints. The outlook so far as life is concerned is good. In some 300 patients admitted to hospital over a period of three years and followed up for an average of nine years, 24 per cent remained fit for normal activities, 40 per cent suffered only moderate impairment of function, 26 per cent were more severely disabled, but only 10 per cent had become helpless cripples. The earlier adequate treatment is instituted, the better will be the prognosis in the individual case.

Juvenile Rheumatoid Arthritis

In children under 5 years of age, in addition to arthritis, there is often splenomegaly, lymphadenopathy, leucocytosis, pyrexia and involvement of the cervical spine. This is the syndrome known as Still's disease. Although growth may be retarded, the condition is usually self-limiting. In older children rheumatoid arthritis gradually merges into the form encountered in adults.

The treatment of Still's disease is that of rheumatoid arthritis but in addition educational facilities are essential when long-term hospitalisation is necessary. Corticotrophin and corticosteroids are effective but their use in treatment is limited by the same considerations already discussed in relationship to rheumatoid arthritis and by the risk of retarding growth.

Felty's Syndrome

The association of lymphadenopathy, splenomegaly and neutropenia with rheumatoid arthritis constitutes Felty's syndrome. Infected skin lesions and septicaemia may occur. Thrombocytopenia is not uncommon. The neutropenia and thrombocytopenia may respond to ACTH if not to corticosteroids, and in some cases splenectomy is undertaken.

Sjögren's Syndrome

Sjögren in 1933 described a group of patients in whom dryness of the eyes and mouth was associated with polyarthritis of the rheumatoid type. Keratoconjunctivitis sicca develops as a result of reduction in the secretion of tears, and xerostomia follows involvement of the salivary glands. Mucus secreting glands of the upper respiratory tract are commonly affected, resulting in recurrent respiratory infections. Not infrequently there is loss of hair and atrophic changes in the nails.

The diagnosis depends on the demonstration of diminished lacrymal secretion and the presence of ulcers on the cornea. The sheep cell test is positive in the majority of cases. Treatment is essentially the same as that outlined for rheumatoid arthritis. Topical application of hydrocortisone eye drops (1·5 per cent) has proved useful in controlling local inflammation in the eye. Artificial tears (methycellulose drops) may also be required in more severe cases and may be combined with sealing of the lacrymal puncta.

Ankylosing Spondylitis

The disease, a progressive inflammatory arthritis of the spinal articulations, affects persons between the ages of 20 and 40. Males are involved about ten times more commonly than females. The disease presents many of the features of an infective process. The ESR may be rapid and low-grade pyrexia is not uncommon in the active phase. However, no specific organism has been isolated and the aetiology of the disease is unknown. The sensitised sheep cell test is negative in virtually all established cases.

Pathology. Biopsy material from cases in which the peripheral joints have been affected shows changes similar to those found in rheumatoid arthritis. Bony ankylosis, however, occurs more frequently in ankylosing spondylitis. Radiological changes are seen first in the sacro-iliac joints, which show irregularity of the joint margins. There is an increase in density of the bone adjacent to the joints. Later the sacro-iliac joints become ankylosed and the vertebral ligaments show progressive ossification (bamboo spine).

Clinical Features. The onset is often insidious. A history of repeated attacks of backache in a healthy young male should always suggest the possibility of ankylosing spondylitis. Radiological examination of the lumbar spine and sacro-iliac regions should never be omitted in such cases. Early morning pain and stiffness are characteristic features. As the disease progresses there is increasing stiffness of the whole spine. Involvement of the costo-vertebral joints gives rise to marked limitation in chest expansion. In milder cases the spine may become rigid without much deformity. In more severe cases kyphosis involving the cervical, dorsal and lumbar spine is not uncommon. Such patients are severely incapacitated, and if the hips become affected they may be rendered helpless. In a small proportion of cases the disease involves the peripheral joints, in which the changes closely resemble those found in rheumatoid arthritis. Iritis occurs in between 25 and 30 per cent of cases and may occasionally be the first sign of the disease. Rarely, aortitis followed by aortic regurgitation develops, usually in the later stages of the disease. Ankylosing spondylitis may be associated with either Crohn's disease or ulcerative colitis.

Differential Diagnosis. Osteoarthrosis of the spine may give rise to pain and limitation of movement. This disease seldom gives rise to symptoms before the age of 50. It is not accompanied by signs of systemic disturbance and the two conditions are readily differentiated by radiological appearances. In osteoarthrosis the sacro-iliac joints are rarely involved, the intervertebral spaces are commonly diminished due to degenerative changes in the discs, and exostoses develop at the edges of the vertebral bodies. Protrusion of the nucleus pulposus of an intervertebral disc can also affect young men and present with backache. Scoliosis and sciatic pain are common in protrusion of intervertebral discs and are rare in ankylosing spondylitis.

Treatment. Radiotherapy is the treatment of choice in the active phase of ankylosing spondylitis. In early cases the results are excellent and the disease process is apparently arrested. Even in more advanced cases with fixed deformities much benefit may result. The incidence of leukaemia is significantly increased following radiotherapy (3 per 1,000 cases treated); but in active cases this risk is outweighed by the good results obtained. In all cases exercises for strengthening the spinal muscles and mobilising the costo-vertebral joints should be prescribed. In the more advanced cases a spinal support may be required to maintain reasonable posture. Deformity of the spine may be corrected by the use of serial plaster shells. Where such correction is not possible and where the deformity is marked, spinal osteotomy may allow the patient to regain a reasonable posture. Where the hips have become affected, surgery has now much to offer (p. 777). The general measures described in the treatment of rheumatoid arthritis should be used in the acute phase, but prolonged immobilisation should be avoided. Corticotrophin and corticosteroids are effective in ankylosing spondylitis, but their use in treatment is limited by the same considerations already discussed in relationship to rheumatoid arthritis (p. 774).

Phenylbutazone is particularly effective in relieving the symptoms of this disease. It is worthy of trial in those patients who fail to respond satisfactorily to radiotherapy and where pain cannot be controlled by other analgesics. The dose should not exceed 300 mg daily. Close supervision is required in view of the possibility of toxic effects (p. 774). Indomethacin (100 mg daily) may also be effective.

Prognosis. In early active cases treated by radiotherapy the prognosis is good. Even in more advanced cases the combination of general measures, radiotherapy and orthopaedic procedures can do much to restore these patients to a reasonable level of function.

Systemic Lupus Erythematosus

This disease is a diffuse disorder involving connective tissue in many parts of the body. The appearance in the blood of immunoglobulins, such as the anti-nuclear factor, has given rise to the hypothesis that the disease may be due to an immune response to autoantigens. The incidence of systemic lupus is considerably higher than was thought in the past, due largely to more accurate diagnosis since immunological tests for lupus erythematosus became available.

A number of factors appear to precipitate the onset, or precede exacerbations. These include unaccustomed exposure to sunlight, infection, periods of emotional stress and the administration of drugs such as sulphonamides, penicillin, procainamide, isoniazid and anti-convulsants. Oral contraceptives may occasionally precipitate the disease in predisposed subjects.

Clinical Features. Young women are predominantly affected. The most common presenting features are fever and an acute migratory arthralgia resembling rheumatic fever, erythematous eruptions on the face and hands, excessive fatigue, malaise, weight loss, anorexia and rapid ESR; anaemia, often haemolytic in type, is frequently present with leucopenia and, more rarely, hrombocytopenia accompanied by bruising and haemorrhage. The occurrence of proteinuria, retinal exudates, pleural effusion, pneumonia, pericarditis or endocarditis indicates the diffuse nature of the disease. A small proportion of patients develop an erosive arthritis of the rheumatoid type. Diffuse or local alopecia often develops. The diagnosis should always be considered in any patient with arthralgia or arthritis associated with a rash of 'butterfly' distribution on the face, especially if fever and signs of visceral involvement are present.

Although fulminating cases occur, the disease usually runs a more chronic course, periods of activity alternating with remissions of varying length. Renal failure is the most common cause of death. The presence of proteinuria early in the course of the illness is of serious prognostic significance.

Diagnosis. An antibody to nuclear material (antinuclear factor-ANF), demonstrable by immunofluorescence techniques, is present in the great majority of cases. While failure to detect this factor is against the diagnosis of systemic lupus erythematosus, it can be found in other conditions, notably rheumatoid arthritis.

Further diagnostic evidence can be obtained by the demonstration of the LE factor in the serum of the majority of cases in the active phase of the disease. This more specific test also depends on the presence of an abnormal immunoglobulin with an affinity for the nuclei of cells. Normal leucocytes, incubated in serum of patients with the disease, extrude nuclear material which is phagocytosed by other leucocytes. These cells, containing amorphous inclusion bodies of altered nuclear material, present a typical appearance on staining. These 'LE cells' are not absolutely diagnostic of systemic lupus erythematosus as they are found occasionally in rheumatoid arthritis, particularly in patients with severe systemic disease.

Treatment. In the presence of acute manifestations corticosteroids are the treatment of choice. Severe symptoms can be controlled but large doses may be required (prednisolone 40-60 mg daily). At this dosage the incidence of serious side-effects is high and the dose should be gradually reduced until an effective maintenance level is reached, usually 10-20 mg daily. Care must be exercised in the use of corticosteroids in the presence of renal or myocardial involvement, as hypertension not uncommonly develops.

In the subacute or chronic forms many observers have reported good results from the use of chloroquine in doses of 250-300 mg daily. This drug has proved valuable in controlling the lesions of the skin.

Dermatomyositis

This rare disease is characterised by focal or segmental necrosis of voluntary muscles sometimes preceded by infiltration with inflammatory cells. Later there may be an increase in fibrous tissue between the muscle fibres or calcification may occur. Two forms of the condition have been described but intermediate grades also occur.

1. Acute dermatomyositis, most common among children, in which oedema, tenderness, swelling and weakness of the proximal muscles of the limbs are

accompanied by fever, leucocytosis and an erythematous skin eruption. A common clinical manifestation is oedema of the eyelids with a characteristic heliotrope discolouration. Involvement of the respiratory muscles may rapidly lead to a fatal termination, but in other cases the acute phase subsides, leaving deformity of the limbs due to contracture of fibrous tissue in the muscles.

2. Chronic dermatomyositis, which runs a more prolonged course, and involves especially the peripheral muscles. Lesions of the skin are not always present and in such cases the term '*polymyositis*' is used (p. 908). This is the type most commonly seen in adults. It may be associated with malignant disease, especially of the gastrointestinal tract.

The diagnosis is confirmed by the finding of raised serum creatine kinase, by abnormal potentials on electromyography or by muscle biopsy. In acute cases the response to corticosteroid therapy may be dramatic and even life-saving. Large doses may be required initially (60 mg prednisolone daily) which are then slowly reduced. In the self-limiting form of the disease, complete withdrawal may be possible. In others maintenance therapy is required (10 mg prednisolone daily). Response in the more chronic cases is usually unsatisfactory. A combination of splints and physiotherapy is used to prevent or correct deformity. Occasionally, calcified deposits may be removed by oral treatment with diphosphonate compounds.

Scleroderma

In this disease the collagen fibres of the dermis first become swollen, then dense and sclerotic, giving rise to contractures and deformities of the joints. Changes are most prominent in the hands and face. The pathology is not confined to the skin. In progressive cases the alimentary tract, lungs, myocardium and kidneys may be affected (*systemic sclerosis*). Blood vessels in the skin and viscera show marked intimal thickening. Intercurrent infection, and cardiac or renal failure are common causes of death. Treatment is unsatisfactory. The corticosteroids are of little value. It is claimed that d-penicillamine (p. 877) can soften the skin in some cases. Every effort must be made to prevent crippling deformities of the peripheral joints by the use of splints and physiotherapy, but care must be exercised in the use of all forms of heat because of the marked impairment of the circulation to the skin.

Polyarteritis

This condition is described on page 305.

Polymyalgia Rheumatica

This descriptive term has been applied to a syndrome which is characterised by pain and especially stiffness affecting mainly the muscles of the shoulder and pelvic girdles. It is accompanied by marked systemic disturbance in the form of mild fever, weight loss, increased ESR and moderate anaemia. Swelling of the sternoclavicular joints is not uncommon. Transient swelling of the knees and occasionally of other joints may occur. Limitation of movement in the shoulders may arise insidiously and persist for several months. Polymyalgia rheumatica affects the middle-aged to elderly and women more often than men. The aetiology is unknown but in some cases there is evidence of cranial (giant cell) arteritis (p. 306) and biopsy of the temporal artery may provide confirmation of the diagnosis. Symptoms may persist for many months but usually then subside without residual disability.

Treatment. This should follow the lines used in other forms of non-articular rheumatism, i.e. rest and full doses of analgesics. Should improvement not occur within a week or 10 days, and particularly when systemic symptoms are marked, 15-20 mg of prednisolone should be given daily in divided doses. When symptoms are controlled the dose should be gradually reduced, first by 2·5 mg every few days, then by 1 mg weekly. Complete withdrawal is possible within four to six months in the majority of cases. When signs of arteritis are present prednisolone should be given at once in doses of 30-40 mg daily and maintained until symptoms are fully controlled. Withdrawal should be even more gradual in these patients.

Gout

Gout is a disease characterised by recurrent attacks of acute pain and swelling at first affecting only one joint, usually the metatarso-phalangeal joint of the big toe, later becoming polyarticular. Although primary gout is the result of an inborn error of purine metabolism, it is described in this section because its principal clinical features are connected with the locomotor system.

Aetiology

1. *Hereditary Factors.* Primary gout is undoubtedly a hereditary disorder. A family history of the disease is obtained in from 50 to 80 per cent of cases.
2. *Age.* The disease is infrequent before the age of 40.
3. *Sex.* Gout is a very rare disease in women.
4. *Diet.* In the past it was believed that an excessive intake of foods high in purines was the primary and essential cause of gout. This view is not now accepted, although there is some evidence to suggest that an acute attack can be induced by a high purine diet in patients predisposed to gout.
5. *Secondary gout* may occur as a complication of haematological disorders such as polycythaemia, leukaemia and myelofibrosis, and following administration of drugs, notably thiadiazine diuretics and frusemide.

Precipitating Factors. An acute attack may be precipitated by dietary indiscretions including over-indulgence in alcohol and an idiosyncrasy to certain foods. An attack may also be precipitated by injury, excessive exercise, intercurrent infection and surgical operations.

Pathology. Urates are deposited in the articular and periarticular tissues, the extra-articular cartilages of the ears (tophi), and the kidneys. The deposits lead to absorption of bone and give rise to the cyst-like appearances or punched-out areas seen in radiographs. There is an inflammatory reaction in the synovial membrane. As the disease progresses the articular cartilage becomes eroded and thinned. Urates are deposited in the subchondral bone and synovial membrane. Finally the changes of osteoarthrosis appear.

Clinical Features

Acute Form. The big toe is the first joint to be affected in over 90 per cent of cases. The onset is sudden; the patient is commonly awakened through the night by excruciating pain; the joint becomes red, swollen, hot and exquisitely tender. The neighbouring veins are distended. The appearance of the joint may suggest a pyogenic infection or local cellulitis. Gout should always be borne in mind when these symptoms appear for the first time in a middle-aged male. Pyrexia, sweating, loss of appetite, constipation and scanty, highly coloured urine are common accompaniments of the acute attack. Blood examination may reveal a polymorph leucocytosis and a rapid ESR. After a few days the pain decreases. The skin over the affected joint becomes scaly and itchy. In the early stages of the disease the attacks occur at long intervals. Between attacks the patient is free from symptoms and radiological examination reveals no change in the affected joint. During the acute attack the plasma uric acid is raised, but may return to normal between attacks. The normal value of the plasma urate (uric acid) in the male is 2-7 mg/100 ml (uricase method). In women it is slightly lower.

Chronic Form. Attacks occur more often and are of longer duration. Finally a stage is reached where remissions between the attacks are incomplete and there is persistent pain and stiffness with deformity of the affected joint. The arthritis becomes polyarticular, the ankles, hands and wrists being first affected, then the knees, elbows, shoulders and hips. Tophi begin to appear in the periarticular tissues and the cartilages of the ears. These consist of deposits of urates of chalky consistency.

Complications. In the late stages signs of progressive renal failure may appear, and examination of the urine reveals protein, casts and red blood cells. Excessive excretion of uric acid may lead to calculus formation and attacks of renal colic. These calculi are not radio-opaque. Atherosclerosis and hypertension may complicate the picture, and death from coronary thrombosis or cerebral thrombosis may occur. In chronic gout the plasma uric acid is continuously high.

Diagnosis. The diagnosis may be made on a history of acute recurring attacks of arthritis with complete remissions, usually occurring in a male between 30 and 50 years of age. A family history of gout is frequently obtained. In early cases the plasma uric acid may be normal between attacks and radiological examination negative. In later cases a high plasma uric acid combined with typical radiological findings will confirm the diagnosis.

It is important to bear in mind the fact that gout may be the first manifestation of the myeloproliferative disorders already mentioned.

Treatment

ACUTE ATTACK. Until recent years colchicine was the most effective drug available for controlling the acute attack of gout, but in the doses required frequently caused severe gastrointestinal upset. It has been shown that phenylbutazone is even more effective and it is now the drug of choice. It should be prescribed in doses of 600 mg daily for two to three days then reduced to 300 mg until pain disappears. Corticotrophin or corticosteroids will be required only in exceptional cases of gout which fail to respond to the administration of phenylbutazone. Indomethacin is also effective but is liable to cause severe headache and gastrointestinal symptoms in the doses necessary to suppress symptoms.

CHRONIC GOUTY ARTHRITIS. *Uricosuric Agents.* Prolonged administration of drugs which increase the excretion of uric acid leads to a diminution in the number of acute attacks, a lowering of the blood uric acid, a decrease in the size of tophi, and may diminish the incidence of renal damage. The drugs of choice are probenecid in doses of 0·5 g three or four times daily and sulphinpyrazone in doses of 200-400 mg daily. Experience has shown that acute attacks may become more frequent during the early stages of uricosuric therapy, but their incidence can be reduced by the administration of colchicine 0·5 mg two or three times daily. Ample fluids should be taken to prevent the deposition of urates or uric acid in the kidney. Since salicylates antagonise the uricosuric action of these drugs, their coincidental use must be forbidden.

Allopurinol. This drug inhibits the enzyme xanthine oxidase responsible for the conversion of xanthine and hypoxanthine to uric acid. Thus the level of plasma uric acid falls and the excretion of its precursors is increased. These are more soluble and have a higher renal clearance rate than uric acid. The level of serum uric acid can be reduced to normal levels by a dose of 300 mg daily. As is the case with all drugs which markedly reduce the level of serum uric acid, fluctuations, particularly a rapidly falling level, may be associated with acute attacks of gout. Accordingly, colchicine 0·5 mg three times a day should be prescribed along with allopurinol during the first two or three months of treatment. Allopurinol has already been shown to be remarkably free from toxic effects, mild rashes being the most common.

Special indications for the use of allopurinol are:

1. Severe tophaceous gout,
2. Gout not controlled by uricosuric drugs,
3. Intolerance of uricosuric drugs, e.g. allergy,
4. Where there is excessive overproduction of uric acid,
5. A history of repeated uric acid stone production,
6. Gout with advanced impairment of renal function, and
7. Uric acid nephropathy which may occur during the treatment of leukaemia or the reticuloses with radiotherapy or cytotoxic drugs, when massive amounts of uric acid may have to be excreted.

Diet. Dietary restrictions are no longer considered to be of primary importance in the treatment of gout except in the presence of obesity where appropriate restrictions should be imposed. However some patients find that attacks of gout are precipitated by consuming certain wines, spirits or foods rich in purine (sweetbreads, liver, kidney, brain, heart, small fatty fish, fish roe, meat extracts). These patients should be advised to exclude the offending substance from the diet.

Other Measures. In cases with damaged or deformed joints the physiotherapeutic measures described for the treatment of rheumatoid arthritis should be applied. When tophi have become large or have ulcerated through the skin, they should be removed surgically.

Pseudo-Gout

(*Chondrocalcinosis*)

In this condition, crystals of calcium pyrophosphate are deposited in cartilage and other articular structures, giving rise to degenerative changes. The cause is unknown but there is a strong familial tendency and the condition is often associated with various other diseases such as hyperparathyroidism and haemochromatosis. Acute episodes which closely resemble true gout occur at intervals. There is no general metabolic disturbance. The synovial effusion contains crystals distinguishable microscopically from uric acid and radiological examination reveals deposits of calcium in the cartilage. Treatment of acute incidents with phenylbutazone, 600 mg daily, reducing the dose as symptoms are controlled, is usually effective. Treatment between attacks is along the lines laid down for osteoarthrosis.

Osteoarthrosis

Osteoarthrosis is characterised by degeneration of the articular cartilage and the formation of bony outgrowths at the edges of the affected joints. Usually only one or two of the larger joints are involved. The condition occurs amongst elderly people of either sex but may appear at any age in a joint which has been damaged by disease or injury.

Aetiology. Osteoarthrosis arises as a result of an exaggeration of the normal ageing process in the joints. When one joint is particularly affected a history is frequently elicited of an injury to that joint some years before. Malalignment, following fractures of the long bones, frequently gives rise to osteoarthrosis in adjacent joints. Symptoms are prone to develop in weight-bearing joints and in those joints subjected to excessive strain. Thus, osteoarthrosis of the hips, spine or knees is particularly common in those engaged in heavy labour, and in obese subjects. It is a disease associated with advancing years, and in most patients symptoms do not appear before the age of 50.

Pathology. There is patchy degeneration and splitting of the articular cartilage at the points of maximum weight-bearing, with exposure of the underlying bone, which tends to become denser and harder. New bone is laid down at the edges of the joints, resulting in the formation of osteophytes. Bony ankylosis never occurs, although limitation of movement may be very marked.

Clinical Features. The joints most frequently involved are those of the spine, hips and knees. The symptoms are gradual in onset. Pain is at first intermittent and of an aching character, appearing especially after the joint has been used, and relieved by rest. As the disease progresses, movement in the affected joints becomes increasingly limited, at first by muscular spasm and later by the loss of joint cartilage and the formation of osteophytes. There may be repeated effusions into the joints, especially after minor twists or injuries. Crepitus may be felt or even heard. Muscular wasting is always present to a greater or lesser extent. This is an important factor in conditioning the progress of the disease, as in the absence of normal muscular control the joint becomes more prone to injury. In the majority of patients the disease is confined to one or two joints, especially the hips or the knees.

A clinically distinct form of osteoarthrosis occurs mainly in middle-aged females as a familial trait and has been termed *primary generalised osteoarthrosis.* The terminal interphalangeal joints of the fingers are commonly affected, cartilaginous or bony outgrowths appear on the dorsal aspect of these joints (Heberden's nodes) and may give rise to considerable deformity and at times pain, but little disability. The first carpometacarpal joints, apophyseal spinal joints, the hips, ankles and knees may also be involved.

Diagnosis. There is usually little difficulty in distinguishing the condition from rheumatoid arthritis, in which there is evidence of a general systemic disturbance and characteristically the proximal interphalangeal and metacarpophalangeal joints are involved. It must be borne in mind, however, that in long-standing cases of rheumatoid arthritis osteoarthritic changes may appear in the affected joints. Degenerative changes not uncommonly appear in the joints in gout.

Radiological Examination. There is characteristically a loss of joint space, and some sclerosis of the articular margins. In more advanced cases osteophytes appear at the bone edges.

Course and Prognosis. The rate of progress will depend on the amount of use to which the affected joints are put. It must be borne in mind that degenerative changes are present in the joints of most people over the age of 50 years, but only a few complain of any symptoms. The pain in osteoarthrosis is probably due to changes in the joint capsule and periarticular tissues.

Treatment. The pathological changes in osteoarthrosis are irreversible, but much may still be done to alleviate symptoms, especially in the early stages of the disease. Much will depend on the social circumstances of the case and whether undue stresses and strains can be removed from the affected joints by a change of occupation or transfer to lighter work. The institution of rest periods during the day may greatly alleviate pain and stiffness. The patient may require to give up unduly strenuous hobbies. The fitting of rubber heels to the footwear may help by reducing jarring and minimising the risk of slipping. In obese patients the most important single form of treatment is to obtain a substantial reduction in weight, especially in cases where the hips or knees are affected. When pain is a prominent symptom rest in bed is required, combined with local heat and gentle active exercises. Full doses of analgesics such as aspirin and codeine should be given. Phenylbutazone (p. 774) may be effective in relieving pain where other measures have failed. It should be used with caution. Hydrotherapy is of benefit in cases of osteoarthrosis. Gentle movement of the joint under water relaxes spasm of muscles, diminishes pain and increases the range of movement. In cases where one hip or one knee is dominantly affected, arthrodesis of the joint will provide a stable pain-free joint. Arthroplasty has also been used with success in osteoarthrosis of the hip and knee.

The intra-articular injection of corticosteroids (p. 775) has been followed by improvement in a proportion of cases. Results are most favourable in the knee, but less satisfactory in the hip. Improvement may be maintained by injections given at intervals of one to three months. Patients should be warned to avoid excessive use of weight-bearing joints during the period following injection.

Miscellaneous Lesions of Connective Tissue

Many people suffer episodes of pain and stiffness of acute or insidious onset for which no obvious cause may be found. The most common sites are the neck, shoulder girdle, spine and gluteal regions. Muscle spasm of reflex origin is a prominent feature and accounts for the stiffness which must be differentiated from limitation of movement due to joint damage. Absence of signs of systemic illness and a normal ESR distinguishes this group of conditions from diffuse diseases of connective tissues. Terms used in the past such as fibrositis, muscular rheumatism, neuralgia and panniculitis are best discarded.

Certain factors may be of importance in precipitating attacks in susceptible individuals. Exposure to cold and damp has always been suspected as a cause of ‘rheumatic’ complaints. Unaccustomed physical effort, undue fatigue, minor injuries and poor posture have also been incriminated. Complaints become more common with increasing age. Any reduction in muscular efficiency will render an individual more prone to strain or injury of tendons, ligaments and extra-articular soft tissue structures. Pain arising from such deep structures is poorly located, and referred diffusely to the overlying skin. Probably the most important cause underlying many such complaints is a loss of efficiency of the spinal shock absorbers, the intervertebral discs. Loss of resilience and elasticity occur long before radiological evidence of disc degeneration becomes apparent and the interfacetal joints of the spine are more exposed to strains and sprains. Pain may be referred from the cervical intervertebral joints to the occipital region, shoulder girdle and arm. Lumbago and sciatic pain without signs of root pressure are most commonly due to reduced capacity of the disc system to withstand acute stress or more chronic strain caused by poor posture, flabby muscles or obesity. Occupational factors are of great importance. Sickness absence attributable to ‘rheumatic’ complaints is much higher among miners, dockers and foundry workers than it is among employees in light industry or clerks.

Diffuse muscular pain and stiffness is common in certain infections, particularly of viral origin, such as influenza, rubella and measles. Epidemic myalgia (*Bornholm disease*) is due to a virus of the Coxsackie group and is characterised by fever accompanied by intercostal or abdominal pain. The illness may last for 5 to 10 days but occasionally continues for several weeks. Epidemics of stiff neck have also been attributed to a viral infection.

Many tense and anxious people complain of aches and pains, particularly in the region of the neck, shoulders or lower back. The emotional disturbance is reflected in the physical state of the patient.

Clinical Features. The presenting features are pain accompanied by muscle spasm and limitation of movement. The onset may be acute or insidious. In acute cases the patient may be severely incapacitated. When the condition is subacute or chronic, pain and stiffness are most marked after a period of inactivity and may be eased by moderate exercise. Tender areas may be present, sometimes referred to as myalgic lesions, but such areas of local tenderness can be reproduced by injection of an irritant into deep structures, such as the interspinous ligaments and cannot be regarded as of pathogenic significance. The clinical symptoms are variable depending on the site of the underlying cause.

Diagnosis. It is essential to carry out a careful and detailed clinical examination as a great many diseases of diverse origin frequently present with musculoskeletal symptoms. Too often a diagnosis of 'fibrositis' is made in patients suffering from metabolic bone diseases, such as osteoporosis or osteomalacia or from hyperparathyroidism. Myalgia or myopathy may be an early sign in both local and diffuse malignancies. It is important to distinguish pain and stiffness of psychogenic origin.

Treatment. In all cases the cause must first be sought and, if possible, removed. The vast majority of patients will make a good recovery if treatment is adequate, but inaccurate diagnosis may lead to prolonged incapacity.

In the obese patient the most important measure is to secure a reduction of weight. An endeavour should be made to prevent further attacks by correcting faulty posture and by giving advice regarding the avoidance of chilling and excessive physical fatigue. In cases with signs of root pressure, due to lesions of the intravertebral discs, a period of rest combined with graduated exercises for the extensor muscles of the spine will be required. In some cases a support for the cervical or lumbar spine will control symptoms. In others, with persistent evidence of root involvement, surgery may be indicated (p. 894).

When pain is severe full doses of an analgesic (p. 773) will be required. Local symptoms are greatly eased by the application of some simple form of heat by means of a hot water bottle or electric blanket. When areas of acute local tenderness are present, the injection of 2-3 ml of local anaesthetic (1 per cent of procaine) may be followed by marked relief of pain. Injection may have to be repeated once or twice to obtain the maximum benefit. Infiltration should be followed by heat, massage and active exercises. Local pain throws the musculature out of balance, and if this is not corrected postural changes may be produced, causing a recurrence of symptoms.

In certain more chronic cases hydrotherapy provides heat combined with active movement and this is often effective where other measures have failed.

Prognosis. Most cases run a short acute course and are symptom-free in one to two weeks. A proportion of cases become chronic, especially if treatment of the initial attack has been inadequate.

DISEASES OF BONE

Metabolic and Endocrine Diseases

Rickets (p. 137) and *osteomalacia* (p. 142), *osteoporosis* (p. 144), *hyperparathyroidism* (p. 649) and *Cushing's disease* (p. 656) all show an impairment of the composition of bone which is reflected in decreased density on radiological examination and in a liability to pathological fractures.

Infections

Osteomyelitis is most commonly encountered in children under the age of 12. *Staph. pyogenes* is the cause in the majority of cases and in about half of these has its origin in a boil or a superficial staphylococcal infection. Thence there is a haematogenous spread to the metaphyseal region of a long bone. In children the onset is often abrupt with fever, nausea and severe pain at the site of infection. Occasionally indolent infections of bone become localised and persist for long periods—the so-called Brodie's abscess. The more chronic forms are now relatively rare.

The most effective treatment, particularly early in the disease, is the administration of lincomycin (p. 101).

Tuberculosis may affect the anterior aspects of one or more vertebral bodies and the intervening intervertebral discs. The vertebrae later collapse causing a kyphosis usually in the thoracic region. Tuberculosis of the spine is now uncommon in Britain.

Tumours

Simple tumours and primary malignant disease, such as osteogenic sarcoma, are much less frequently encountered than secondary carcinoma from primary growths, most commonly in the lung, breast, prostate, thyroid or kidney. The first clinical manifestation of the carcinoma may be a pathological fracture or the patient may complain of diffuse discomfort which may be dismissed by the doctor as 'rheumatic'. In contrast the patient may be symptomless and yet metastases may be widespread throughout the skeleton and seen on radiological examination as multiple osteolytic or osteosclerotic areas. Myelomatosis (p. 755) may present in similar ways; early diagnosis is important as this condition can be controlled with chemotherapy. Oestrogen therapy or surgery, such as orchidectomy or oophorectomy, may be helpful in the management of metastases from the prostate or breast and local radiotherapy may be a useful palliative measure when pain is a problem, wherever the primary carcinoma may be situated or even if it cannot be identified.

Diseases of Unknown Aetiology

Paget's Disease of Bone

(*Osteitis Deformans*)

The incidence of this common condition increases with advancing years, and it is seldom seen before the age of 50 years. Both sexes may be affected. Histologically and radiologically there is evidence of increased osteoblastic and osteoclastic activity as indicated by areas of increased bone formation and density alternating with areas of rarefaction. The lesions may be found in the pelvis, skull, humerus, spine, femur, tibia or elsewhere. The distribution is characteristically irregular, so that normal bone may be found between affected areas.

Clinical Features. Many patients have no symptoms and the disease is recognised accidentally only when radiological examination is made for some other reason. In others, pain in the affected bones occurs and occasionally is severe; sometimes the affected areas are tender on pressure. They may be unusually warm on palpation, due to the increased vascularity of the lesions. When the skull is involved, headache may be troublesome; hearing may be impaired from compression of the auditory nerve. Deformity of bones may occur when the condition is advanced. Fractures may occur spontaneously or after minor trauma but usually heal normally. Osteogenic sarcoma is an uncommon late complication of the disease.

Rarely the bone lesions are so widespread and so vascular that they form, in effect, an arteriovenous shunt. The cardiac output is therefore increased, and in some patients heart failure may ultimately appear.

Chemical Pathology. The serum calcium and phosphorus concentrations are normal, except during periods of immobilisation, when they may be considerably raised. The serum alkaline phosphatase concentration, which in these circumstances is a measure of osteoblastic activity, may be increased to as much as 725 i.u./*l* (100 King-Armstrong units/100 ml) or more.

Treatment. Little can be done to alter the course of the disease. It is liable to be of long duration and is often accompanied by apparent remissions. Symptomatic treatment for pain in the bones or headache may be required, and if fractures occur they should be treated as if the bone were otherwise normal. Calcitonin (p. 648) is known to afford relief in those patients with much pain and the diphosphonates have been effective in some cases.

PREVENTION OF DISEASES OF CONNECTIVE TISSUE, JOINTS AND BONES

As the aetiology of the chronic inflammatory and degenerative diseases of connective tissue is largely unknown, preventive measures are limited. However, much can be done to avoid the exacerbation of an existing disability. Morbidity can be limited if excessive use of an arthritic joint is avoided. In all disorders involving the locomotor system it is mandatory that obesity be corrected, not only because of immediate benefits but because timely action may prevent the later development of osteoarthrosis in a vulnerable joint. The adjustment of faulty posture removes stresses which in the long-term could cause degenerative changes in affected structures. The correct treatment of fractures and congenital deformities will obviate the mechanical strains which may predispose to degenerative joint disease.

The risks of powerful modern drugs must be kept constantly in mind. Gout may be precipitated by excessive use of diuretics and in predisposed individuals, systemic lupus erythematosus may be provoked by a variety of commonly used drugs. As the treatment of the connective tissue disease involves the use of various potentially dangerous drugs, awareness of the hazards of therapy is particularly important. Aspirin can cause severe gastrointestinal bleeding. Analgesic nephropathy is a rare but serious condition. Phenylbutazone and gold have many adverse effects and may cause death from pancytopenia. Also, leucopenia in rheumatoid arthritis is accompanied by risks of septicaemia and pyoarthrosis, often unrecognised, particularly in patients treated with corticosteroids. Injudicious corticosteroid therapy can create more problems than it solves and the decision to use corticosteroids on a long-term basis carries also the responsibility for the early recognition of the undesirable effects of such therapy.

J. J. R. DUTHIE.
J. N. MCCORMICK.

Further reading:

Boyle, J. A. & Buchanan, W. W. (1971). *Clinical Rheumatology*. Oxford and Edinburgh: Blackwell.
Copeman, W. S. C. (1969). *Textbook of Rheumatic Diseases*, 4th ed. Edinburgh: Livingstone.
Hollander, J. L. & McCarty, J. R. (1972). *Arthritis and Allied Conditions*, 8th ed. London: Kimpton.
Mason, M. & Currey, H. L. F. (1970). *An Introduction to Clinical Rheumatology*. London: Pitman.

Diseases of the Nervous System

THE approach to patients presenting neurological problems must follow a logical course. Clinical examination reveals neurological signs which reflect disordered neural function. The nature and distribution of these signs depend on the anatomical localisation of lesions within the central nervous system. It is a fundamental error to relate particular signs to specific pathological processes. Paralysis of one side of the body, hemiplegia, may equally well arise from a stroke or from a cerebral tumour since both lesions may similarly interrupt motor pathways. It is the history of the neurological illness which indicates the nature of the pathological process involved. A careful chronological assessment of the way in which a neurological disability has developed is essential if a diagnosis is to be made. Attention to the symptoms and signs which indicate loss of function of particular parts of the nervous system then follows for purposes of localisation.

Lesions which suddenly affect the nervous system, cause maximal disability within a few hours and after a static period of days or weeks then show a tendency to improve are usually due to vascular disturbances and sometimes to trauma. Disabilities of insidious onset and slow but inexorable progression are often due to degenerative disorders or to tumours of the central nervous system. A remittent history, wherein episodes of disability are followed by periods of improvement, with later recurrence of symptoms elsewhere in the nervous system, is characteristic of disseminated sclerosis. Inflammatory lesions such as infections often develop rapidly, but less acutely than traumatic or vascular catastrophes, and the recovery phase is also usually rapid. Some conditions are characterised by paroxysmal short-lived disorders of function, followed by rapid and complete recovery. A history of this type may be due to epilepsy or migraine or to transient ischaemic attacks. These general principles are a useful guide but atypical presentations occur. Sometimes a neoplasm may produce very rapid deterioration and occasionally repetitive, minor vascular lesions give rise to a progressive, 'step-wise' deterioration of function.

Some diseases cause systematised affection of cells or fibres of similar type; these conditions, of which motor neurone disease is a good example, usually result in bilateral and symmetrical dysfunction. Tumours produce progressive involvement of adjacent neural structures causing clinical disabilities which may later be accompanied by symptoms resulting from the occupation of space by the tumour within the confines of the skull or the spinal canal.

A neurological diagnosis is achieved by the integration of all the information gained from the patient's history, the general medical examination and the neurological examination.

APPLIED ANATOMY AND PHYSIOLOGY

The Motor System

Movements, whether voluntary or involuntary, are the result of the contraction or controlled relaxation of groups of muscles and never of a single muscle only.

They are effected by contraction of muscles which act as prime movers and reciprocal relaxation of their antagonists. The action of the prime movers is provided with a firm base by contraction of synergists which stabilise the joints, and by appropriate adjustments of posture. The postural adjustments are largely under the control of the extrapyramidal motor system and the vestibular and spinal reflexes. Voluntary movements require the participation of the precentral gyrus of the cerebral cortex ('motor area') and the timing and degree of contraction or relaxation of the muscles of the synergy are coordinated by the cerebellum, especially when a movement involves more than one segment of a limb. The activities of the upper motor neurones from the motor area of the cortex, the extrapyramidal motor system and the cerebellum influence, directly or indirectly, the cells of the anterior horn of spinal grey matter or motor cranial nuclei from which the lower motor neurone runs to a group of muscle fibres ('motor unit'). Thus the lower motor neurone is the 'final common path' for all efferent impulses directed at the muscle and the groups of anterior horn cells may be considered to 'represent a muscle' in the same sense as the cells of the motor cortex 'represent a movement'. This distinction is vital to an understanding of the signs and disorders of the motor system.

Upper Motor Neurone. The fibres arise from cells in the precentral gyrus ('motor area'). These initiate movements of different parts of the opposite side of the body, the parts being represented in the following order from below upwards—tongue, face, hand, forearm, arm, trunk, thigh, leg, foot and perineal areas with considerable overlap. The cortical area representing movements of each of these parts is proportional to its functional importance rather than to its anatomical size. The projections of the upper motor neurones to the contralateral motor nuclei of the brain stem and anterior horn of the spinal cord are shown in Figure 89.

A destructive lesion of the indirect corticospinal tract above its decussation causes a loss of some voluntary movements of part of the opposite side of the body, according to the fibres involved, but automatic associated movements, such as the stretching of a paralysed arm when yawning, may persist and other voluntary or reflex movements using the same lower motor neurones and muscles may be preserved. This is the essential difference between paralysis of upper motor neurone type and that due to a lower motor neurone lesion. For the same reason stretch reflexes are retained but these are usually of heightened activity. This indicates that the pyramidal tract normally carries fibres which are inhibitory to the stretch reflex. The pattern of cutaneous protective reflexes also changes, causing the emergence of an extensor plantar reflex. There are thus two types of disturbance, a negative one due to loss of a particular activity, and a positive one due to the release of lower levels from control. Hughlings Jackson considered this to be a principle of general application in the nervous system and the concept is important in understanding the signs of pyramidal disease. Another type of positive symptom results from irritative lesions (usually incomplete damage to a nerve cell or its fibre) which cause spontaneous activity of the affected neurones. Spontaneous activity in upper motor neurones causes involuntary movements as in focal epilepsy (p. 829).

SIGNS OF A LESION OF THE UPPER MOTOR NEURONE. These are:

1. Weakness or paralysis of movements of part of one side of the body. (Other movements using the same muscles may be spared.)

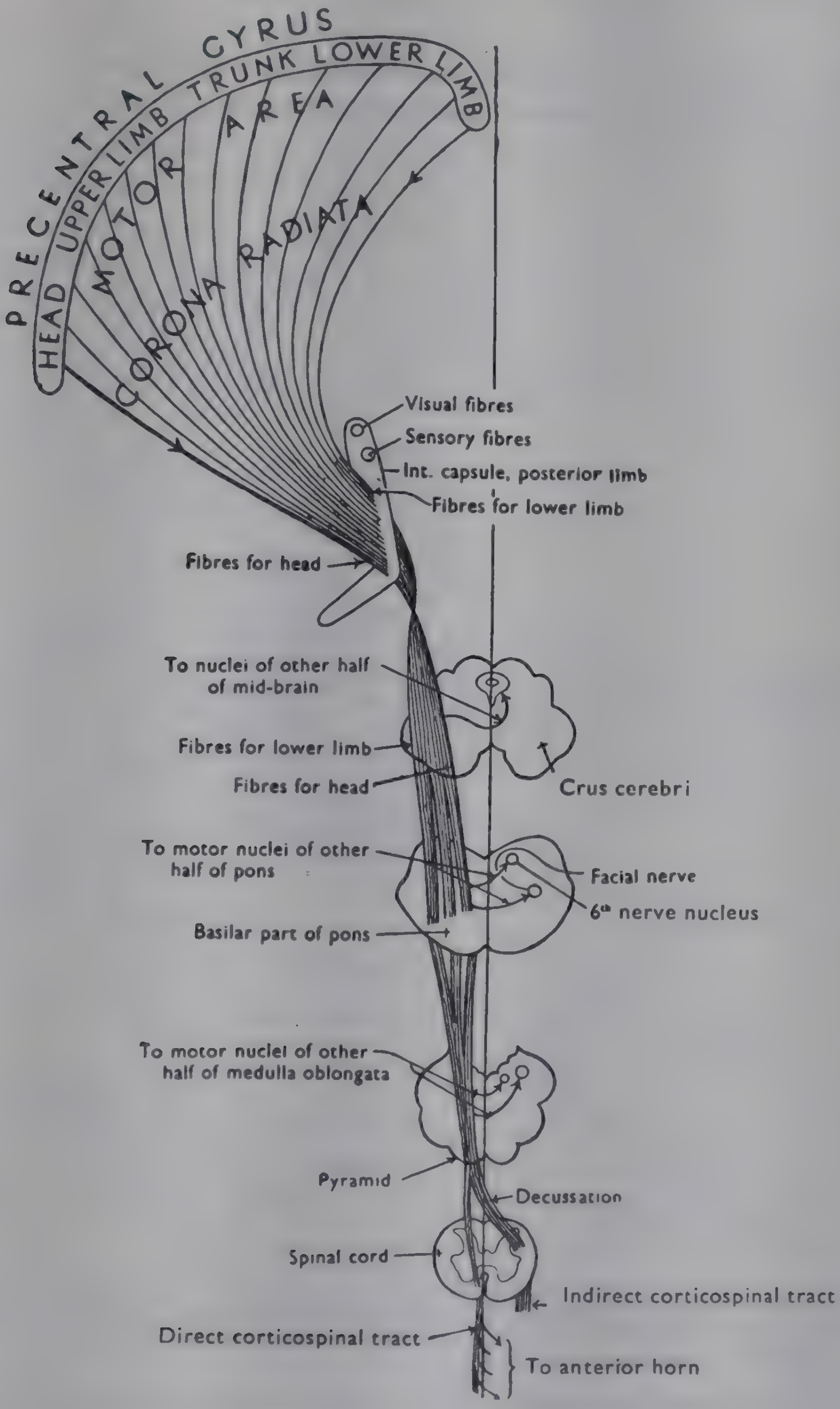


FIG. 89

THE MOTOR PATHWAYS

2. Increase of tone of spastic type. This is characterised by an increased resistance to passive movement, which is maximal at the beginning of movement, smoothly sustained, and suddenly lapses as passive movement is continued ('clasp-knife phenomenon'). It occurs predominantly in flexor muscles in the upper limbs and extensor muscles in the lower limbs (the antigravity muscles).

3. Increase in amplitude of tendon reflexes; clonus may be present.
4. Loss of the abdominal reflexes.
5. An extensor plantar response (Babinski reflex).
6. No muscle atrophy apart from slight wasting which may occur as a result of disuse.
7. Normal electrical excitability of the involved muscles (p. 798).

These signs occur with disease involving any part of the upper motor neurone from the cortex down, but the exact level at which the lesion lies may be determined by the upper level of increased reflexes and by associated features.

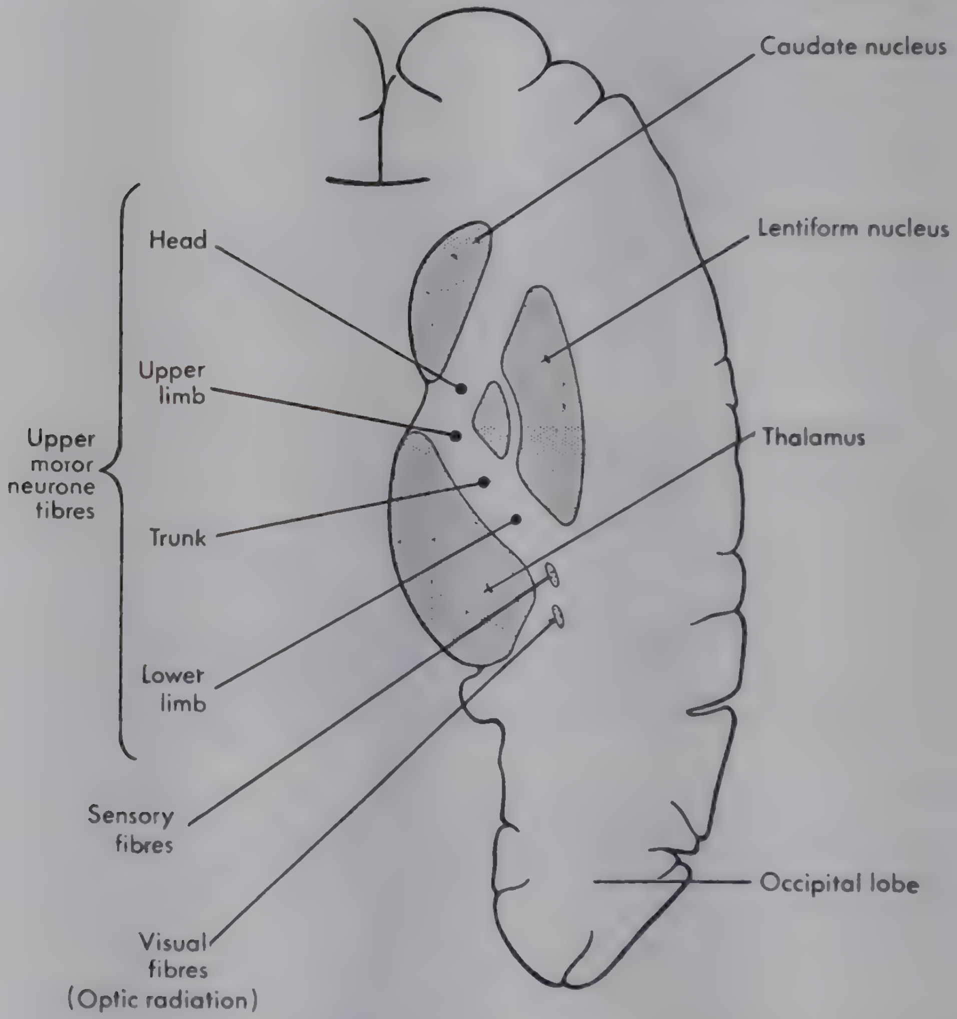


FIG. 90

SCHEMATIC HORIZONTAL SECTION THROUGH THE RIGHT CEREBRAL HEMISPHERE SHOWING POSITION OF SOME OF THE FIBRES IN THE INTERNAL CAPSULE

Cortex. Localised paralyses, affecting for example, one limb only, are characteristic of lesions at the cortical level. The upper motor neurones are spread over a wide area and only very large lesions could cause a hemiplegia. There may be associated evidence of cortical dysfunction such as dysphasia and focal epileptic fits sometimes occur.

Internal Capsule. As pyramidal fibres here are closely packed, a hemiplegia is likely, with involvement of face, arm and leg on the opposite side. There may be hemihypaesthesia and hemianopia from damage to adjacent sensory and visual fibres (Fig. 90).

Brain Stem. Lesions in this area are rarely confined to the pyramidal tract. A common presentation comprises affection of one or more cranial nerves on the side of the lesion and signs of an upper motor neurone lesion on the opposite side.

Spinal Cord. The pyramidal pathways may be affected bilaterally. The level of the lesion in the cord is often delineated by accompanying lower motor neurone signs or by sensory disturbance or loss of tendon reflexes, which indicate a segmental localisation.

Lower Motor Neurone. Axons emerge from the cells of the anterior horn of the spinal cord and from the nuclei of the motor cranial nerves and pass through the anterior nerve roots to enter a mixed peripheral nerve in which they run to the muscles which they supply. There are two types, a large fibred (alpha) efferent neurone and a small fibred (gamma) efferent neurone (Fig. 91). The term 'lower motor neurone' is usually confined to the large fibred system. Each lower motor neurone has a terminal branching so that it is distributed to the motor end-plates of a group of muscle fibres. The anterior horn cell, the axon and a group of muscle fibres comprise the motor-unit and each muscle is composed of a large number of such units. The anterior horn cell is activated by impulses from the corticospinal tracts, from the extrapyramidal tracts, and from some afferent fibres of the posterior nerve root responsible for spinal reflexes. The lower motor neurone (alpha efferent fibre) is thus an integral part of the spinal reflex arc and is the final common pathway for all motor impulses, involuntary or voluntary, directed to a muscle. Normal nutrition of a muscle appears to depend on its contact with the spinal cord through the lower motor neurone since if it is interrupted the muscle rapidly wastes.

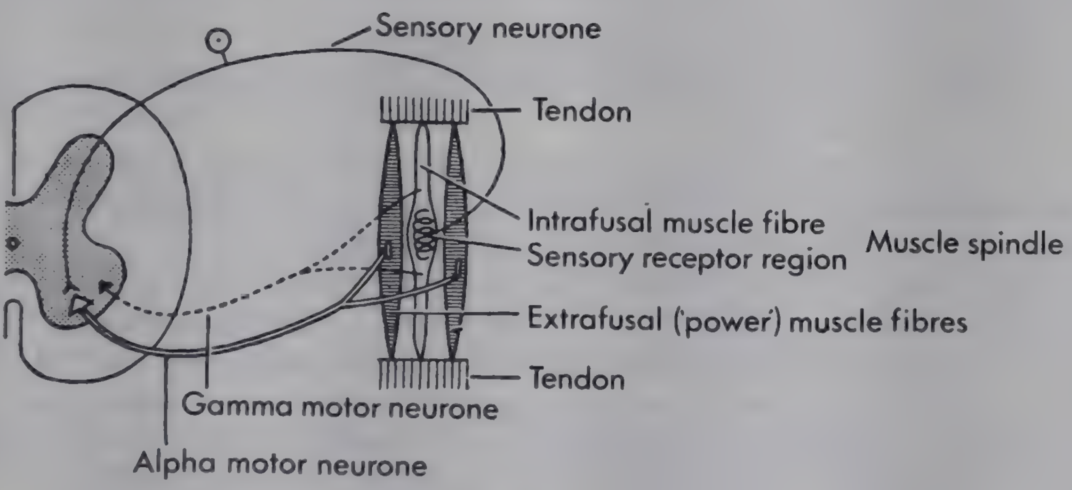


FIG. 91

THE LARGE (ALPHA) AND SMALL (GAMMA) EFFERENT NEURONES AND THE STRETCH REFLEX ARC

A system of small motor neurones (gamma efferent fibres, Fig. 91) arising from cells in the anterior horn of the spinal cord runs with the lower motor neurones (alpha efferent fibres) to the intrafusal muscle fibres of the muscle spindles. By their activity they cause these specialised muscle fibres to contract.

The resulting tension on the muscle spindles makes them more sensitive to any stretch applied to the whole muscle and so they sensitise the stretch reflex arc. Activity in these fibres is regulated by supraspinal influences from the anterior lobe of the cerebellum and the reticulospinal system and is affected in disorders of the cerebellum and extrapyramidal motor system. The small efferent system is important in the regulation of muscle tone. It may be utilised for controlled voluntary movements, the corticospinal activity first passing to the intrafusal muscle fibres of the spindles. The latter respond to the tension induced and in turn activate the alpha motor neurones which cause the main muscle fibres to contract.

SIGNS OF A LESION OF THE LOWER MOTOR NEURONE. The following signs will be present only in those muscles supplied by the particular neurones affected:

1. Weakness or paralysis of muscles. This affects all movements in which they take part whether as prime movers or synergists, voluntary or involuntary, or in reflex contractions.
2. Loss of tone on passive movement (flaccidity).
3. Wasting of the affected muscles which appears within two or three weeks of an acute lesion (atrophy).
4. Absence of reflexes subserved by the affected neurones. Abdominal and plantar reflexes remain normal unless the neurones to the appropriate muscles are damaged and then these reflexes cannot be elicited.
5. Single muscle fibres contract spontaneously when they are no longer influenced by their associated lower motor neurone. This phenomenon, called fibrillation, is detectable by electromyography but is invisible through the skin. Lower motor neurones which are damaged but still able to conduct impulses may give rise to spontaneous contractions of bundles of fibres in the muscles supplied. Such contractions (fasciculation) are often visible (p. 882).
6. Contractures of muscles due to replacement by fibrous tissue and 'trophic' changes such as dryness and cyanosis of the skin, and brittleness of the nails, partly due to impaired circulation.
7. The electrical excitability of the peripheral nerves and muscles is altered as can be shown by special tests. They may usefully be combined with electromyography to confirm that a weak and wasted muscle is denervated. Lesions of peripheral nerves short of complete interruption may cause slowing of conduction which can be measured by special techniques.

If lower motor neurones are damaged in the cord or nerve roots the muscles and reflexes affected in the ways described above will be those supplied by one or more segments of the spinal cord. If the neurones are damaged more peripherally after they have been redistributed in the nerve plexuses, the paralysis will occur in the territory supplied by the appropriate peripheral nerve and it is probable that there will be similar damage to the sensory fibres with which they are associated in the mixed nerve.

Extrapyramidal System. This is a complex neuronal network, extending from the cortex to the medulla, from which emerge descending spinal pathways whose influence on lower motor neurones modifies voluntary motor activity. Interspersed in this latticework of fibres are areas of grey matter. Some of these are but loose aggregations of nuclei in the reticular formation of the brain stem, but there are also several well defined nuclear masses called the basal ganglia, which include:

1. The corpus striatum comprising the caudate nucleus and putamen.
2. The globus pallidus or pallidum.
3. The substantia nigra.
4. The subthalamic nucleus.

There are rich interconnections between the constituents of the basal ganglia and thence via the ventro-lateral nucleus of the thalamus to the extrapyramidal areas of the cortex and to the medullary reticular formation. The normal functions of the extrapyramidal system are ill-understood. Dysfunction due to disease gives rise to impaired voluntary movement, alteration of tone, and involuntary movements.

DISTURBANCE OF VOLUNTARY MOVEMENTS. There is no true paralysis in extrapyramidal disease, but rather slowness of movement and poverty of movement in that spontaneous gestures, changes in facial expression, and associated movements for postural adjustment such as swinging the arm when walking are lost on the side opposite to the lesion.

DISTURBANCE OF TONE. Tone may be increased as in Parkinsonism or decreased as in chorea. Increase in tone, of extrapyramidal type, has characteristic features. It is present throughout the whole range of passive movement; it affects opposing muscle groups equally; it may be smooth and plastic ('lead-pipe rigidity') or intermittent ('cog-wheel rigidity') which is more common.

INVOLUNTARY MOVEMENTS. There are many varieties but four important types may be described. Some involuntary movements such as focal epilepsy, tics and fasciculation are not extrapyramidal in origin and are excluded from this list.

1. *Tremor*. This consists of rhythmic movements caused by alternate contraction of opposing groups of muscle. Tremor at rest is typical of Parkinsonism.
2. *Choreiform Movements*. These are quasi-purposive, non-repetitive jerky movements of face, tongue or limbs. They give the impression that some action is about to be undertaken, but is suddenly broken off by interposition of another purposive movement.
3. *Athetosis*. Athetoid movements are slow, sinuous writhing movements of the face and limbs, being most marked peripherally.
4. *Dystonia*. Movements resembling athetosis but much slower affect the proximal parts of the limbs and the trunk which tends to rotate ('torsion spasm'). The movements are so slow that they may cause prolonged abnormal postures.

Cerebellum. The cerebellum is the most important part of the nervous system for the coordination of movement and the muscular contractions required to maintain posture. The cerebellum receives impulses from many sources, principally the proprioceptive end-organs, the skin, the vestibular nuclei and the cerebral cortex. The pontine nuclei and the inferior olive relay fibres from the cerebral motor cortex and basal ganglia respectively to the cerebellar cortex of the opposite side. The cerebellar cortex integrates this information about body posture, limb position and motor intention and sends efferent fibres via the cerebellar nuclei to the reticular formation, red nucleus and vestibular nucleus of the opposite side, whence fibres descend to influence both types of motor cells in the anterior horns of the spinal cord; as these descending fibres cross again each cerebellar hemisphere controls the ipsilateral side of the body. Efferent fibres from the cerebellum also ascend to the contralateral thalamus through which the cerebral cortex is influenced. The cerebellum is therefore a great coordinating centre controlling the synergic action of muscles during voluntary and automatic movements as well as adjusting posture. It determines whether a movement will be carried out by the lower motor neurones directly or by the slightly slower but more controlled indirect route through the small efferent system and the peripheral reflex arc (p. 797). Disturbance of the latter route lowers the excitability of tendon reflexes.

The effects of disease of the cerebellum are best seen in acute lesions, for in chronic lesions considerable compensation occurs so that the deficit is less than might be expected. A lesion of the cerebellar hemisphere produces all its effects on the same side of the body. The principal effects are:

MUSCULAR HYPOTONIA. The muscles are flaccid on palpation, show diminished resistance to passive movement and, when an outstretched limb is suddenly displaced, it makes a greater excursion than usual and oscillates before resuming its posture.

DISTURBANCE OF TENDON REFLEXES. The reflexes are either diminished or pendular as when the knee jerk is followed by a series of diminishing oscillations.

DISTURBANCE OF POSTURE AND OF GAIT. The head may be tilted towards the side of the lesion and the patient leans or may even fall towards that side. His gait is reeling and he tends to stagger to the side of the lesion.

DISORDERS OF MOVEMENT. Incoordination, hypotonia and the fact that muscular contraction is unregulated by the muscle spindles cause ataxia which manifests itself in different ways:

Dysmetria. Movements are not accurately adjusted to their object, so that the finger may overshoot or fall short of the object it is required to touch. If a movement is attempted with the eyes closed the finger overshoots towards the side of the cerebellar lesion ('past-pointing').

Dyssynergia. Movements involving more than one joint are broken up into their component parts.

Intention Tremor. A combination of dyssynergia and dysmetria causes faulty correction of the badly directed limb movement so that it approaches the target in a zig-zag manner. The coarse irregular tremor increases as the target is approached. It is not increased when the eyes are closed. The contraction of muscles necessary to maintain a posture may be similarly affected so that tremor at rest occasionally occurs in cerebellar disorders.

Dysdiadochokinesis. The arrest of one movement and its immediate replacement with the opposite movement requires accurate coordination of the various muscles of the synergy. Rapidly alternating movements are therefore disturbed and carried out in a clumsy, irregular, jerky fashion.

Rebound Phenomenon. For the same reason a strong contraction cannot be arrested when resistance is suddenly removed, whereupon the limb shoots beyond the normal range.

Disorders of Articulation and Phonation. Articulation is irregular, slurred and explosive as the volume of sound is poorly controlled. A rarer form of dysarthria is scanning-speech in which the syllables tend to be separated from each other.

Disturbance of Eye Movements. Jerking nystagmus in the horizontal plane is commonly seen. It is a defect of postural fixation involving conjugate gaze (p. 818). In a unilateral cerebellar lesion the movements are greater in amplitude and slower in rate when the eyes are deviated to the side of the lesion.

The Sensory System

Superficial sensation which arises from the skin has four primary components, touch, pain, warmth and cold. *Deep sensations* arising from subcutaneous structures are deep pain, pressure and proprioception which enables the recognition of movements of joints and the position of the parts of the body relative to one another. Vibration is a sensation due to rhythmical stimulation of groups of deep and superficial touch receptors. Some of the afferent impulses carried in 'sensory' nerve fibres do not reach consciousness but convey impulses directly or indirectly to motor neurones for reflex functions or to the cerebellum for purposes of coordination, e.g. impulses arising in muscle and tendon receptors. All sensory impulses arise in the sensory receptors or end-organs which are widely distributed throughout the body. It is probable, though debatable, that specialised receptors respond to specific types of stimuli. Stimulation of an end-organ causes impulses to pass along the first sensory neurone to the spinal cord. This neurone has its cell body in a dorsal root ganglion but does not synapse until it reaches a second order neurone in the spinal cord or brain stem. On entering the cord by the posterior nerve root, fibres subserving proprioception, vibration and a proportion of touch sensation turn medially and ascend in the posterior column of the same side to the lower part of the medulla oblongata to synapse with cells in the gracile and cuneate nuclei. From there, the second order neurone crosses to the other side of the medulla and ascends in the medial lemniscus to the main sensory nucleus of the thalamus. Fibres subserving pain, warmth, cold and the remainder of touch sensation synapse in the posterior horn of the spinal cord soon after entering it. Most of the second order neurones cross at the same level, or one or two segments higher, to reach the anterolateral column where they ascend to the thalamus as the spinothalamic tract. Some of these fibres do not cross but enter the ipsilateral spinothalamic tract. As it ascends through the brain stem the tract gradually intermingles with the medial lemniscus and terminates along with it in the main sensory nucleus of the thalamus. Third order neurones, maintaining their functional specificity, are then relayed from the thalamus to the sensory area of the cortex which is situated in the postcentral gyrus.

Areas of the sensory cortex representing the different parts of the body are arranged in a similar manner to the motor cortex. Some appreciation of sensation is possible at the thalamic level but the cortical projection is necessary to allow discrimination of the intensity and pattern of stimulation. From the postcentral gyrus further connections are made with other parts of the cortex, particularly in the parietal lobe where the information derived from superficial and deep sensation is integrated so that judgement of the size, shape, weight, texture and pattern of objects is possible. This sensory information is also integrated with information derived from the special senses to provide a mental picture of the body (body image). This synthesis is mainly carried out in the non-dominant parietal lobe. The corresponding part of the left cerebral hemisphere is important for other mental functions in which recurrent patterns of stimulation achieve the status of symbols and so are used for the receptive and interpretative aspects

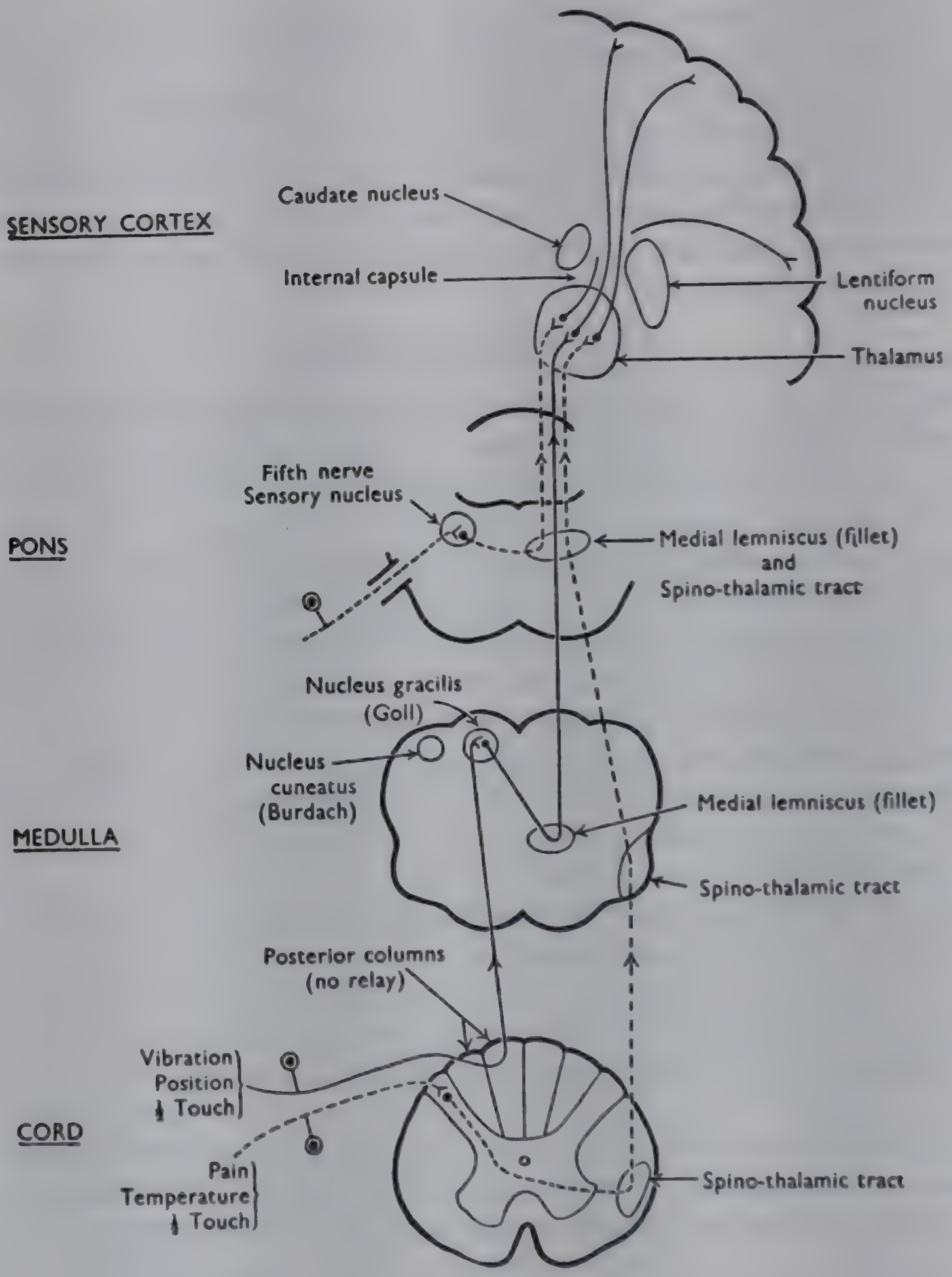


FIG. 92

DIAGRAM OF THE MAIN SENSORY PATHWAYS

of speech functions. For this reason it is usually called the dominant or major hemisphere (in some left-handed people speech is mainly represented in the right hemisphere). This important part of the parietal lobe is connected with the lower part of the motor cortex of the same side so that patterns of lip, tongue, respiratory and finger movements may be used to convert ideas into motor symbols, the motor side of speech. An understanding of the link between symbol and meaning requires a knowledge of the physiological basis of the mind which we do not have at present.

Most of the afferent signals entering the central nervous system never reach consciousness. Some are used for spinal reflexes and make contact directly or through interneurones with motor neurones. Other fibres which also originate in muscle receptors end at the base of the posterior horn in contact with second order neurones. These neurones turn laterally to the periphery of the cord to ascend in the anterior and posterior spinocerebellar tracts to the cerebellar cortex. Most of these ascend without crossing but some second order neurones cross to the opposite anterior spinocerebellar tract. These fibres carry some of the proprioceptive information required to enable the cerebellum to coordinate limb movements. Still other sensory fibres, which do not carry 'sensation' in the ordinary sense, are extremely important for the maintenance of consciousness. These are collateral branches of the main spinothalamic pathways and of the special sensory tracts which turn medially into the upper part of the reticular formation in the mid-brain. Here there is a chain of short neurones with intimate interconnections which also receives neurones from most parts of the cerebral cortex. It is therefore an important integrating centre. At its upper end it communicates with the non-specific nuclei of the thalamus which relay impulses to all areas of the cortex. Activity in this system is considered to be essential for the conscious state and may be important in some mental functions in collaboration with the cerebral cortex.

Disease of the sensory system may be accompanied by positive phenomena such as pain or paraesthesiae due to spontaneous activity or irritation of sensory neurones, or by negative phenomena in which there is loss of the ability to appreciate some modality of sensation (anaesthesia and analgesia). These symptoms occur only with disorders of the first or second order neurones, i.e. from the end-organs to the thalamus. Suprathalamic lesions show certain differences. Paraesthesia may occur with irritative lesions of the sensory cortex but anaesthesia does not. Instead there is a loss of sensory discrimination and of the spatial and quantitative aspects of sensation.

Peripheral Nerve. With a complete lesion all forms of sensation are lost in the area supplied by the affected nerve, but the zone of anaesthesia may be limited by the fact that neighbouring nerves overlap into its territory, the extent varying from person to person. The resistance of different types of fibres to disease need not be the same so that it is common for one type of cutaneous or deep sensation to be more affected than another and indeed some may be spared. If the afferent fibres of a reflex arc are affected, as the sciatic nerve in the ankle jerk, the reflex concerned is lost. Some neuropathies do not affect individual nerves but rather damage fibres selectively. As a general rule the longest fibres are most susceptible and so the sensory and motor disturbance is first noticed at the tips of all the toes and fingers, irrespective of nerve supply, and spreads proximally as the advancing disease involves progressively shorter fibres. This produces a 'glove and stocking' distribution of sensory loss.

Posterior Root. The different forms of sensation are affected by a posterior root lesion in the same way as for a peripheral nerve but the distribution of the loss follows a dermatome pattern. The overlap from adjacent roots may be so great that no anaesthesia can be detected. When the root is irritated pain and paraesthesia are experienced in the full dermatomal distribution of the root and pain may also be experienced in the deep structures such as muscles and ligaments which are supplied by the root. (These structures do not necessarily underlie the dermatome.) Any reflex subserved by the involved root is also lost, for example, the ankle jerk when the S 1 posterior root is damaged by a prolapsed intervertebral disc.

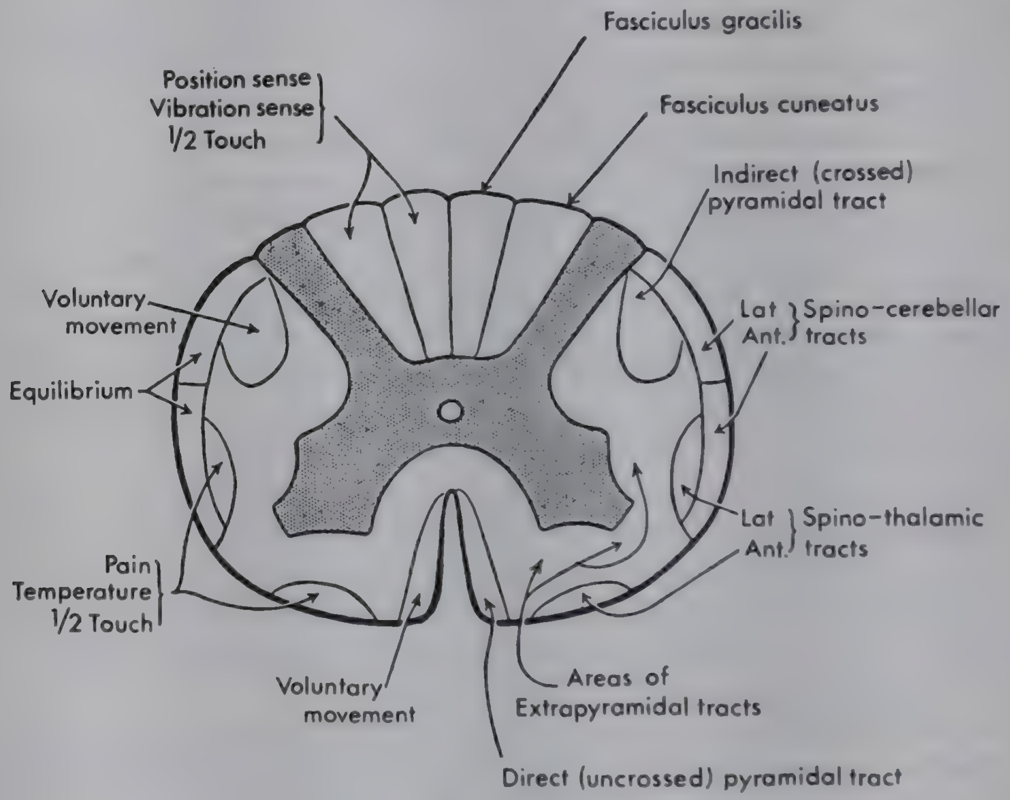


FIG. 93

CROSS-SECTION OF SPINAL CORD

Posterior Column. A lesion confined to the posterior column of the spinal cord will cause loss of position and vibration sense on the same side, but the sensations of pain, touch, warmth and cold will be preserved (Fig. 93). The loss of the sense of position causes sensory ataxia since the patient is unable to control his movements by awareness of the position achieved at each instant. Sensory ataxia differs from cerebellar ataxia in that it is more marked when the eyes are closed, because vision can compensate to a certain extent for loss of proprioceptive information. Thus there is unsteadiness in the finger-nose test which is greater when the eyes are closed but without the marked tremor of cerebellar ataxia. The gait is ataxic and the patient walks with a broad base to give himself a firmer foundation and steps high to make sure that his feet clear the ground which he is unable to feel with certainty. If his eyes are closed he is unable to stand with feet close together without swaying (Romberg's test). Vibration sense is abolished below the level of the lesion ipsilaterally. The same symptoms will be found if the first order neurones of the proprioceptive nerve fibres are damaged peripherally but they will then be associated with other signs of peripheral nerve disease.

Spinothalamic Tract. Lesions of the anterior and lateral spinothalamic tracts in the anterolateral columns of the cord or their continuation through the brain stem cause impairment of the ability to appreciate pain, warmth and cold on the contralateral side of the body below the level of the lesion. Touch is usually modified (it feels 'different') but not abolished because of its alternative pathway in the posterior columns. This is the situation produced by the operation of anterolateral cordotomy for the relief of intractable pain.

Brain Stem. Since the spinothalamic tract and medial lemniscus run close together and eventually intermingle, lesions of the upper brain stem usually affect all forms of sensation on the contralateral side of the body. With mid-brain lesions the hemihypaesthesia will extend to the face, but with ponto-medullary lesions the second order neurones from the trigeminal sensory nucleus or the nucleus and descending tract of the fifth nerve may be damaged so that sensory loss will be on the same side of the face as the lesion but on the contralateral side of the rest of the body (Fig. 92, p. 802).

Thalamus. Lesions of the main sensory nuclei in the lateral part of the thalamus may cause:

1. Spontaneous pain of most unpleasant quality in the opposite side of the body.
2. The threshold for pain is raised on the opposite side of the body but when it is exceeded the resulting pain is exquisite and has the same unpleasant quality which often causes considerable emotional reaction.
3. Loss of other modalities of sensation on the opposite side of the body.

Sensory Cortex. Lesions above the thalamus do not abolish any form of sensation though the threshold may be raised. There is impairment of position sense, of two-point discrimination, of the ability to localise touch and to recognise objects in the palm of the hand (astereognosis) since shape and texture cannot be identified though the patient is able to feel the object. Disturbance of the spatial aspects of sensation is greatest when the parietal lobe is involved, and especially in lesions of the 'minor' hemisphere (p. 802) this may cause disturbance of the body image and of spatial orientation. For instance the patient may be unable to recognise part of his own body on the side opposite to the lesion or may feel that it is distorted. He may ignore one side of external space or of his own body (though he is capable of feeling it) and this is most evident if the unaffected (ipsilateral) side of his body, or visual field, is stimulated simultaneously. When presented with this 'perceptual rivalry' his brain 'ignores' the stimulus on the side contralateral to the affected parietal lobe though a stimulus applied to that part alone would be recognised immediately. Lesions of the dominant hemisphere (p. 803) in the region where parietal, temporal and occipital lobes meet (angular and supramarginal gyri) are associated with receptive dysphasia (p. 810). This is a special case of the failure to analyse the temporal and spatial aspects of sensory stimuli.

The Reflexes

Certain functions are economically catered for by the nervous system by means of reflexes, which are short chains of neurones (the reflex arc) connecting a receptor to an effector organ such as muscle or gland, so that an appropriate stimulus invariably leads to a specific response. The quantity but not the nature of the response may be modified by other stimuli or by supraspinal influences from the cortex, extrapyramidal system or the cerebellum. There are two main categories of reflex—postural and protective. The appropriate stimuli for postural reflexes are muscle stretch and vestibular impulses. Protective reflexes are evoked by stimuli to pain receptors. They are usually superficial (cutaneous or corneal); the protective 'spasm' of muscles around a painful lesion is similar in nature.

Stretch Reflexes (Tendon Jerks). A basic postural reflex depends on the stimulation of muscle spindles when a skeletal muscle is stretched. The afferent fibre enters the cord by a posterior nerve root and communicates directly or via a chain of interneurones with the anterior horn cells which control the stretched muscle, thus causing it to contract and so resist the displacement. A sudden tap to a tendon activates only the monosynaptic arc (in which the afferent fibre terminates at the anterior horn cell without interneurones) and this results in a sharp but brief contraction of the muscle. For the contraction to be sufficient to cause a visible movement the sensitivity of the stretch receptor must be potentiated by contraction of its intrafusal muscle fibres by the activity of the small efferent motor neurones (p. 797). This activity may be increased by certain manoeuvres such as clenching the teeth or pulling the interlocked hands apart. This is termed reinforcement of the reflex and a tendon jerk should not be declared absent until reinforcement has failed to make it visible. The stretch reflex is inhibited by receptors in the tendon (and accessory receptors on the muscle spindles) if muscle tension rises too high, thus risking the integrity of its fibres. This may happen when the reflex is exaggerated by withdrawal of a normal inhibitory effect of the corticospinal tract (p. 794), so that the contraction is abruptly stopped. This is the mechanism of the 'clasp-knife' response. There are also supraspinal facilitatory and inhibitory influences from the extrapyramidal system and cerebellum so lesions of these systems may abolish the reflexes.

An example of a monosynaptic stretch reflex is a knee jerk. A tap on the patellar tendon activates stretch receptors in the quadriceps muscle giving rise to impulses in first order sensory neurones which pass directly to the lower motor neurones to the quadriceps muscle making it contract. A lesion anywhere along this path will cause loss of the reflex, hence it is important in the localisation of disease to know through which spinal segment each reflex passes. The common tendon reflexes are the brachioradialis or supinator (C 5-6), the biceps (C 5-6), the triceps (C 7), the knee (L 3-4) and the ankle (S 1).

Superficial Reflexes. These are polysynaptic reflexes originating from stimuli to superficial structures. The interneurones may connect with motor neurones at several segmental levels and so the response may be a coordinated movement, usually designed to withdraw the stimulated part from a potentially dangerous stimulus. There are very many of these reflexes, some of which are conflicting. For example, stimulation of the sole of the foot evokes both flexion and extension reflexes. Which reflex will predominate is determined by higher influences. The nature of this influence is unknown but is believed to require the corticospinal (pyramidal) tract and damage to this tract will cause a change in the predominant reflex pattern.

PLANTAR REFLEX. When the outer border of the sole of the foot is stroked in normal people after infancy, there is plantar flexion of the great toe. In 1896 Babinski pointed out that when the upper motor neurone was damaged the same stimulus caused dorsiflexion of the toe. (Anatomically this is described as an extensor plantar response though physiologically it is part of the flexion withdrawal reflex.) When the reflex is well developed it can be elicited from the medial side of the sole of the foot or even from the lower part of the leg and the hallux response is accompanied by dorsiflexion and abduction or fanning of the other toes and even withdrawal of the limb. The fundamental importance of the extensor plantar or Babinski response as a sign of loss of function of the upper motor neurone is widely accepted but it may occur in transient form during temporary states such as coma or after an epileptic fit and need not indicate permanent damage. It is often extensor in normal infants during the first year of life.

ABDOMINAL REFLEXES. When the skin on one side of the abdomen is stroked with a pin, there is a reflex contraction of the underlying muscles, a reflex for protection of the viscera. This may be lost on the affected side in disease of the upper motor neurone though the sign is less reliable than the plantar reflex. For instance the abdominal reflexes may be lost early in disseminated sclerosis yet retained despite severe pyramidal tract damage in motor neurone disease. The abdominal reflexes may not be obtainable on either side in elderly, obese or multiparous patients, and may be lost where operative incisions have severed the nerves concerned. The abdominal reflexes are served in their peripheral course by the intercostal nerves arising from segments T 8 to 12.

CORNEAL REFLEX. A light touch on the cornea provokes a blink of the eyelids on both sides. The afferent path for this reflex is the first division of the trigeminal nerve and the efferent path is the facial nerve. Loss of both corneal reflexes is a valuable indication of a deepening level of unconsciousness from any cause but should be elicited with discretion in case of accidental damage to the cornea.

Nervous Control of the Bladder and Rectum

Bladder. The nerve supply to the bladder is derived from three sources:

1. Sympathetic, from the first and second lumbar segment via the inferior hypogastric plexus and hypogastric nerves, which relax the bladder wall and contract the sphincters. (This mechanism, present in many animals, is disputed in man.)

2. Parasympathetic, from segments S 2, 3, 4 via the pelvic nerves (nervi erigentes) which contract the bladder wall and relax the internal sphincter.

3. Somatic, from segments S 2, 3, 4 via the pudendal nerves, which contract the external sphincter of the urethra.

Afferent impulses from the bladder wall travel via the pelvic nerves and from the sphincters via the pudendal nerves. Distension of the bladder activates stretch receptors in the bladder wall and stimulates the parasympathetic fibres by means of a reflex arc through the upper sacral segments of the spinal cord; for example in the infant the bladder empties automatically when distension reaches a certain degree. Subsequently two descending pathways from higher levels assume control, one which inhibits the automatic reflex emptying, and the other which relaxes the inhibition when appropriate. The expression of urine is then promoted by contracting the abdominal and relaxing the pelvic muscles.

Interruption of the sacral reflex arc leads to retention of urine. This is accompanied by loss of bladder sensation if the lesion is on the afferent side of the arc, as in tabes dorsalis. Damage to the anterior sacral nerve roots causes an atonic bladder without loss of sensation ('lower motor neurone paralysis'). Lesions in the spinal cord above the sacral segments may damage the inhibitory fibres, causing urgency, precipitancy or incontinence of urine, or damage to the facilitatory fibres may cause hesitancy or retention. If the higher control is completely lost there is a period of retention with overflow from a passively dilating atonic bladder until the sacral reflex begins to function as in infancy, restoring automatic bladder emptying. The bladder is hypertonic ('upper motor neurone paralysis') and may shrink if this is not prevented. Cerebral lesions at the vertex near the motor or sensory areas may also give rise to incontinence or retention, and with frontal lobe lesions the intellectual disturbance may be associated with failure to inhibit reflex emptying.

Rectum. The rectum has a dual nerve supply from the sympathetic (inhibitory) and the parasympathetic (facilitatory) systems. Disturbances of function similar to those in the bladder occur, but are less severe and more transient.

THE LOCALISING SIGNS OF CEREBRAL DISEASE

The Prefrontal Lobe. This comprises the frontal lobe anterior to the precentral gyrus. It is concerned with some aspects of psychological reactions, notably the ability to make intelligent anticipations of the future, and the emotional correlations of thought. Disturbances of these functions cause vague psychiatric disorders which are difficult to diagnose in the early stages. The patient loses appreciation of the consequences of his actions, fails to take forethought and becomes apathetic or morbidly facetious. With progressing dementia his memory and intellect become impaired. His social sense is also affected; he becomes careless about his dress and appearance and may micturate in public or become incontinent without seeming to care about it. Physical signs are few but there may be generalised convulsions and a grasp reflex may be found in the contralateral hand. With this reflex, the patient involuntarily clutches at an object which is drawn lightly over the skin of the palm between the index finger and the thumb. The contralateral arm may be ataxic if the frontopontine fibres connecting with the cerebellum are interrupted. Expanding lesions of a frontal lobe may compress the underlying olfactory nerve causing unilateral loss of the sense of smell (anosmia). These signs may be missed in a routine examination. It is important, therefore, to search for them when confronted with a patient with early mental changes.

The Precentral Gyrus. Lesions in this region give rise to unequivocal signs. Jacksonian epilepsy (p. 829) is common and monoplegia (p. 976) readily develops. A lesion such as a meningioma arising from the falx cerebri involving the superior ends of both 'motor areas' may give rise to signs of an upper motor neurone lesion in both lower limbs, the upper limbs being spared. When a lesion in the dominant hemisphere extends forwards from the inferior end of the precentral gyrus it gives rise to dysphasia of expressive type (p. 810).

The Parietal Lobe. Lesions of this area may also present with Jacksonian epilepsy, but of sensory type, and in addition there is disturbance of the integrative and localising aspects of sensation on the opposite side of the body (p. 801). Lesions situated more posteriorly in the parietal lobe may cause:

1. Spatial disorientation—lack of the patient's ability to find his way about.
2. Apraxia—loss of the ability to perform a pattern of movements though the patient understands its purpose and has no motor or sensory deficit.
3. Agnosia—loss of the ability to recognise a previously familiar object though the patient has good vision and sensation.
4. 'Sensory inattention' or 'perceptual rivalry'—the patient tends to ignore a cutaneous or visual stimulus on the contralateral side if it is presented simultaneously with one on the same side as the lesion though it is perceived if presented alone. This is most prominent in disease of the non-dominant hemisphere (p. 802).
5. Receptive dysphasia—lesions of the angular and marginal gyri or the posterior temporal-parietal junction cause receptive dysphasia which may be predominantly for written or spoken speech. There may be specialised types of dysphasia such as the loss of ability to count or to recognise parts of the body such as a particular finger.
6. Homonymous hemianopia—deep lesions in the parietal lobe may involve the optic radiation and so cause a contralateral homonymous hemianopia (p. 812).

The Occipital Lobe. Irritative lesions cause crude visual hallucinations such as flashing lights, while destructive lesions cause a contralateral homonymous hemianopia.

The Temporal Lobe. Irritative lesions in the posterior temporal lobe may cause visual sensations which are more elaborate than with occipital lobe irritation. Patterns of moving colours or hallucinatory pictures may be experienced by the patient. A similar lesion of the anterior part of the temporal lobe may cause auditory hallucinations (superior temporal gyrus), gustatory and olfactory hallucinations (uncus) or misinterpretations (illusions) of auditory and visual sensations. These are often associated with altered states of consciousness such as dreamy states, automatic behaviour, temporary upsets of memory (*déjà vu*) or brief amnesia. In affections of the dominant hemisphere there may be dysphasia of receptive type (see below). An important sign easily overlooked is a homonymous upper quadrantanopia due to destruction of the lower fibres of the optic radiation which sweep down into the temporal lobe (p. 811).

Speech

Speech employs verbal symbols to communicate thoughts and information. Coherent speech requires the formulation of propositions, which are translated into conventional symbols, earlier acquired and readily accessible, which then reach external expression by means of an efficient vocalising apparatus. Disease processes may interrupt this sequence at various levels to produce different types of speech defects.

INTELLECTUAL IMPAIRMENT. Speech is deranged as a result of a generalised deficit of intellectual function which prevents the organisation of meaningful propositions. Such a disturbance reflects a diffuse impairment of cortical function which may be a temporary phenomenon in toxic confusional states (delirium) or permanent in dementia.

Dysphasia. This comprises disturbances of the symbolic aspects of language and these arise as a result of damage in or near the cortex of the dominant hemisphere. The nature of the defect varies with the site of the lesion. In *expressive or motor dysphasia* the patient can formulate his thoughts in appropriate words (i.e. internal speech is preserved) but is unable to translate them into corresponding sounds. This occurs despite an intact articulatory system and represents a specialised form of apraxia (p. 809) which results from lesions in the posterior part of the inferior (3rd) frontal convolution. Impaired comprehension of language is called *receptive or sensory dysphasia*. The patient fails to understand or carry out spoken instructions. Internal speech is disturbed and hence there is also impairment of the patient's external speech. This is an agnosic deficit (p. 809) and results from lesions of the posterior part of the upper temporal convolutions and the angular gyrus of the parietal lobe.

In clinical circumstances all the speech areas of the major hemisphere are often injured together, which results in combined receptive and expressive dysfunctions. This picture, called 'global or central dysphasia', is usually due to occlusion of the internal carotid or middle cerebral arteries which supply all the regions concerned with speech.

Dysarthria. Imperfect articulation of speech is called dysarthria. Precise enunciation of words requires normal function and coordination of lips, tongue and palate. Any abnormality thereof results in slurring and distortion of speech. Dysarthria may be due to mechanical derangements such as cleft palate or ill-fitting false teeth. Lesions of muscles, myoneural junctions, or lower motor neurones of lips, tongue or palate will also result in dysarthria as will upper motor neurone and extrapyramidal affections of these structures.

When normal monitoring of speech is disturbed by deafness, dysarthria may ensue. This is particularly liable to occur when auditory feedback is distorted by impaired hearing in early childhood.

Dysphonia. Reduced volume of speech, often accompanied by hoarseness, results from dysfunction of the phonating mechanism. This may be due to weakness of respiratory movements so that air flow across the vocal cords is reduced or to malfunction of the vocal cords. The causative lesion may be in the respiratory musculature, in the peripheral nerves, or in central structures. Thus, for example, bilateral palsies of the recurrent laryngeal nerves cause aphonia. Dysphonia may be part of the picture of a bulbar palsy or it may result from extrapyramidal disease, such as Parkinsonism.

The Visual Pathway

The optic nerve carries second order neurones, the first order neurones being very short fibres within the retina. For much of its length it is surrounded by a protrusion of the meningeal membranes into which cerebrospinal fluid can pass, especially if intracranial pressure is raised. For these reasons the optic nerve is liable to suffer from different pathological states than other nerves. The visual pathway is illustrated in Figure 94. Sensory impulses from the retinae pass along the optic nerves to the optic chiasma where the fibres from the temporal halves of the retinae continue posteriorly in the lateral angle of the chiasma into the optic tracts on the same side. Fibres from the nasal halves of the retinae decussate so that the optic tract carries fibres from that part of each retina which receives light from the contralateral half of the visual field of each eye (the light rays crossing in the refractory media of the eyes). In the same way the light rays from the upper part of the visual field stimulate the lower part of each retina and the fibres arising there remain inferior throughout their further path to the cortex. The optic tracts continue to the lateral geniculate bodies where the fibres concerned with vision synapse and the impulses are relayed along the optic radiations to the calcarine area of the occipital cortex. The uppermost fibres which carry impulses derived from the superior quadrants of each retina (lower quadrants of visual fields) pass directly through the parietal lobe, whereas the lowermost fibres which relay impulses from the lower quadrants of the retinae (upper quadrants of visual fields) sweep downwards and forwards round the temporal horn of the lateral ventricle in the temporal lobe before passing to the occipital cortex. Throughout the whole of the visual pathway fibres from the various parts of each retina maintain approximately the same relationship with each other.

Some fibres originating in the retina and passing centrally in the optic nerve form the afferent limb of the light reflex arc of the pupils. These bypass the lateral geniculate bodies and pass medially to the superior colliculi of the mid-brain where they synapse with neurones which pass to the nuclei of the third cranial nerves on each side. From these nuclei arise the efferent limbs of the light reflex (direct and consensual) to the sphincter muscles of the pupils. No visual stimulus is required for the accommodation 'reflex' of the pupil which is more properly an associated contraction related to the movement of convergence of the eyes. This is believed to involve an unidentified cerebral path and a mid-brain nucleus which controls the pupillomotor cells of both third nerve nuclei. This explains the dissociation between the light reflex and the convergence reflex which may occur in neurosyphilis and other diseases.

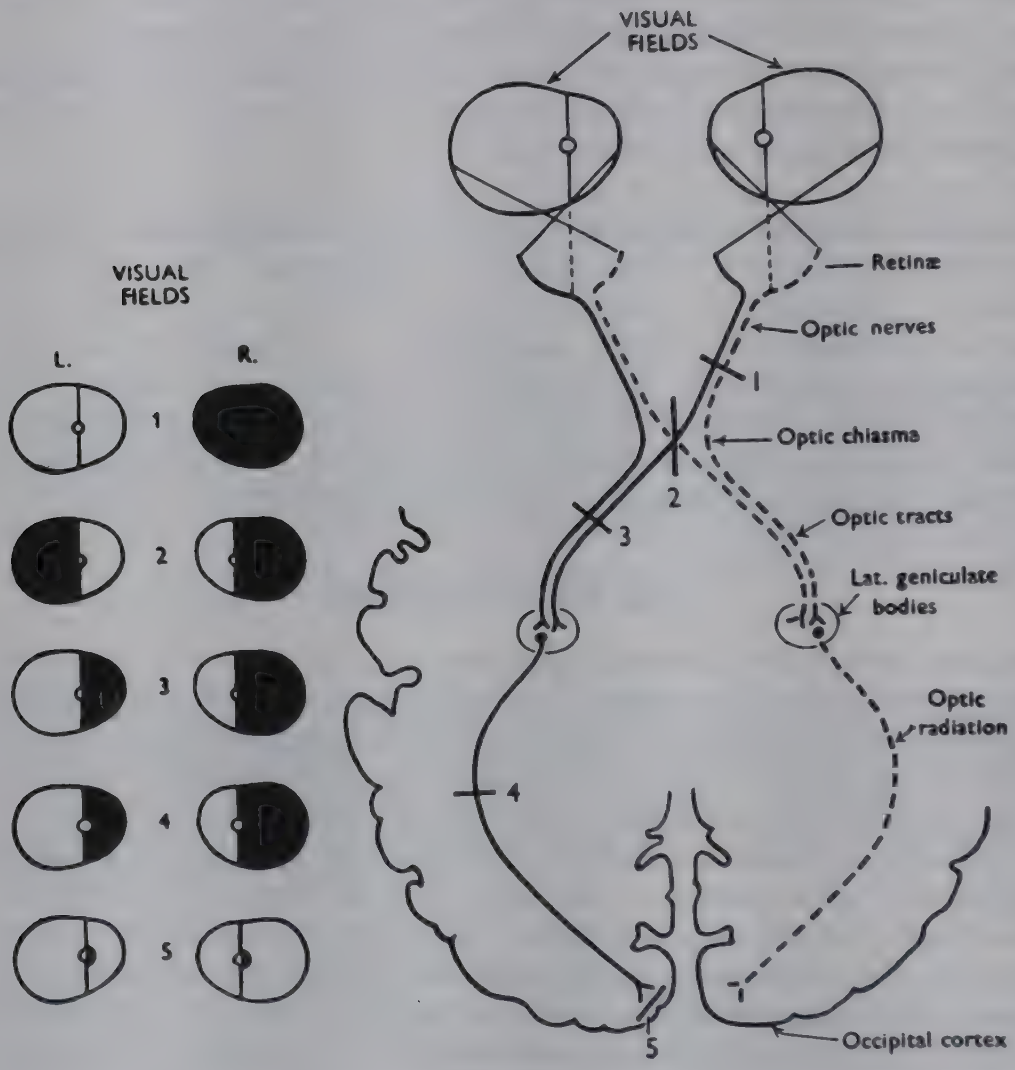


FIG. 94

VISUAL PATHWAYS AND FIELD DEFECTS RESULTING FROM DIFFERENT LESIONS

CLINICAL MANIFESTATIONS OF LESIONS OF THE VISUAL PATHWAY

The Optic Nerve. A complete lesion of the optic nerve produces total loss of vision in the affected eye. There is no light reflex, direct or consensual, when that eye is illuminated but both pupils contract normally when the unaffected eye is illuminated. The pupil may be slightly larger in the blind eye. If the lesion is only partial, islands of loss of vision (scotomata) of various shapes occur in the field of the affected eye. Disorders of the optic nerve are described on page 814.

The Optic Chiasma. A lesion of the central portion of the chiasma involves the decussating fibres from the nasal halves of both retinae and so gives rise to bitemporal hemianopia. In practice such lesions are rarely symmetrical and hence the degree of involvement of the visual fields of each eye is often unequal. A pituitary tumour first compresses the lower fibres and so the bitemporal hemianopia begins in the superior quadrants, whereas a suprasellar cyst compresses the chiasma from above so that field loss starts in the lower quadrants.

The Optic Tracts. A lesion of an optic tract gives rise to a homonymous hemianopia, the lost half of the field of vision of each eye being on the side opposite to the lesion. The involvement of the two fields is often unequal ('incongruous'), being slightly greater in the field of the eye on the side of the lesion.

The Optic Radiation. The effects of a lesion of the optic radiation depend on its exact site. A lesion of the temporal lobe involves the lower fibres only and gives rise to a homonymous defect involving mainly the upper quadrants of the visual fields. A lesion in the anterior part of the parietal lobe causes a homonymous hemianopia mainly affecting the lower quadrants as it affects fibres from the upper parts of the retinae. A lesion at the posterior part of the parietal lobe, where both groups of fibres are again adjacent, gives rise to a total homonymous hemianopia.

The Occipital Cortex. A destructive lesion of one occipital cortex gives rise to a complete (and congruous) homonymous hemianopia if it is extensive, or to a scotoma which is present in the fields of both eyes. Irritative lesions, as in the ischaemia caused by migraine, cause hallucinations of flashing lights which are referred to the contralateral fields of both eyes.

DISORDERS OF THE CRANIAL NERVES

The cranial nerves are frequently involved in generalised disease of the nervous system. In addition, there are specific conditions affecting a single cranial nerve. It is convenient for descriptive purposes to study consecutively the manifestations of lesions of the cranial nerves and their nuclei.

The First Cranial Nerve

The olfactory nerve arises from olfactory receptors in the nasal mucosa. The fine first order fibres pass through the cribriform plate in the floor of the anterior fossa of the skull. They synapse in the olfactory bulb and second order neurones run to the olfactory area of the brain (the anteromedial part of the temporal lobe) and higher autonomic centres by the olfactory tract which lies under the orbital surface of the frontal lobe. Thus tumours of the frontal lobe may compress it and cause loss of the sense of smell (anosmia) on one side of the nose. The fragile fibres passing through the cribriform plate are readily damaged by head injuries.

The Second Cranial Nerve

The anatomy and central connections of the optic nerve are described on page 811 and the visual field changes caused by a lesion of the nerve are discussed on page 812. When the fibres originating in the macular area are damaged there is a loss of visual acuity (amblyopia) which cannot be corrected by lenses. Direct and consensual light reflexes are depressed or absent when the amblyopic eye is stimulated but the convergence pupil response is unaffected.

Papilloedema. This term describes swelling of the optic nerve head (optic disc). The swelling may be due to obstruction to the venous drainage of the retina. Lesions of the optic nerve itself, some of them inflammatory, may also cause swelling of the optic disc which is usually then referred to as papillitis.

The main disorders resulting in papilloedema are:

(1) Increased intracranial pressure due to any cause such as cerebral tumour, cerebral abscess, or meningitis. The rise in pressure of the cerebrospinal fluid causes distension of the subarachnoid space round the optic nerve and compresses the veins.

(2) Obstruction of the venous drainage from the orbit by thrombosis of the central vein of the retina, cavernous sinus thrombosis or, rarely, an orbital neoplasm.

(3) Lesions of the optic nerve such as optic neuritis (p. 815).

(4) Diseases of the retinal arteries such as cranial arteritis.

(5) Extra-cerebral conditions such as malignant hypertension and severe respiratory failure.

The earliest manifestation of papilloedema is engorgement of the retinal veins, followed by an intensified pink colouration of the optic discs and blurring of the disc margin which usually begins on the nasal side. As swelling proceeds the physiological cup is obliterated and the whole optic disc may be elevated. If the papilloedema is severe and particularly when it is of rapid development, there may be accompanying haemorrhages abutting on to the disc (Plate II). If papilloedema is of long standing the disc becomes progressively paler as optic atrophy develops.

Often it is of clinical importance to differentiate the swelling due to raised intracranial pressure from that due to lesions of the optic nerve which present indistinguishable ophthalmoscopic appearances. The visual acuity is usually well preserved when papilloedema is due to raised intracranial pressure whilst optic neuritis usually causes marked loss of visual acuity. Papilloedema due to raised pressure gives rise to early enlargement of the blind spot; chronic severe papilloedema may be accompanied by peripheral constriction of the visual field. Optic neuritis is accompanied by a central scotoma.

Optic Neuritis. This term encompasses inflammatory, demyelinating and some vascular diseases of the optic nerve which, in common, cause loss of vision. In many cases pain in the eye, aggravated by movement and tenderness over the eye, precedes or accompanies the visual disturbance. When the lesion lies anteriorly in the nerve there may be swelling of the optic disc (papillitis). Where the ophthalmoscopic appearances are normal, the lesion lies posteriorly and is called a *retrobulbar neuritis.*

Optic neuritis is most commonly due to demyelination, itself usually a manifestation of disseminated sclerosis, and in this condition recovery of vision within four to six weeks is usual. Rarer causes include vitamin deficiencies, syphilis and toxins, such as methyl alcohol and quinine.

The optic neuritis associated with vitamin B_{12} deficiency and that accompanying excessive smoking of strong pipe tobacco (*tobacco amblyopia*) may have a common pathogenesis. Tobacco smoke contains cyanide which experimentally has been shown to cause demyelination. Hydroxocobalamin, derived from vitamin B_{12}, plays an important part in the detoxication of cyanide. If the intake of vitamin B_{12} is low and cyanide ingestion is high, demyelination of the optic nerve is liable to occur. This is an important observation since tobacco amblyopia may effectively be treated by large doses of hydroxocobalamin.

Optic Atrophy. Loss of fibres in the optic nerve is followed by reactive gliosis and reduced vascularisation. These pathological changes are manifest clinically by pallor of the optic disc and may result from many causes including (*a*) optic neuritis from the various causes listed above; (*b*) pressure on the optic nerve by glaucoma, tumours, aneurysms etc.; (*c*) long-standing papilloedema; (*d*) thrombosis of the central retinal artery; (*e*) trauma; (*f*) genetically determined disorders such as Leber's optic atrophy.

The Third Cranial Nerve

The oculomotor nerve supplies all the external ocular muscles except the lateral rectus and the superior oblique. It also supplies the levator palpebrae superioris, the constrictor of the pupil, and the ciliary muscle. It may be involved in disseminated sclerosis, meningovascular syphilis, diabetes mellitus, and cerebral aneurysms which may compress the nerve at several sites. The manifestations of a third nerve palsy are ptosis, diplopia, external deviation of the eye (divergent strabismus) due to the action of the unopposed lateral rectus muscle and defective ocular movement in the directions in which the muscles supplied by the third nerve move the eye. The patient complains of double vision but in a long-standing lesion one of the images is suppressed. A complete lesion of the third nerve also paralyses the constrictor of the pupil; consequently the pupil is large and fails to react to light (by the direct or consensual path) or on convergence.

The Fourth Cranial Nerve

The trochlear nerve supplies the superior oblique muscle. A lesion of the nerve gives rise to defective movement and diplopia which is maximal when the patient attempts to look down with the eye turned inwards. The pupils are not affected. An isolated lesion of the nerve is rarely encountered, as usually there is also involvement of either the third or sixth nerve.

The Sixth Cranial Nerve

The abducent nerve supplies the lateral rectus muscle of the eye. A lesion of the nerve causes diplopia due to inability to abduct the eye, and deviation of the eye medially (convergent strabismus) due to the unopposed action of the medial rectus muscle. The sixth nerve may be involved by pressure from an aneurysm in the cavernous sinus. Downward displacement of the brain stem due to raised intracranial pressure may stretch the nerve causing a lateral rectus palsy. The causal lesion may lie at a distance from the sixth nerve whose involvement in this manner constitutes a false localising sign.

Diagnosis of Squint. Squint (strabismus) may be paralytic or concomitant.

Paralytic squint is due to weakness of one or more of the extra-ocular muscles. Defective movement of the eye can be seen when the patient attempts to move the eye by the weak muscle and this usually causes diplopia. The rules for identifying the paretic muscles causing diplopia or squint are:

1. The separation of the images is greatest when the patient attempts to look in the direction to which the paretic muscle should move the eye.
2. In this position, the most peripheral image is the 'false image' from the affected eye. It is identified by covering one eye with a green glass and the other with a red one.

Concomitant squint ('lazy eye') is due to failure to maintain the correct posture of an eye which is so defective in vision that its image is suppressed by the brain. There is no muscle paresis and both eyes are capable of full movements in all directions. The most common cause is an error of refraction during childhood. If recognised and properly treated with suitable spectacles the squint can be prevented though a 'latent squint' often remains.

CONJUGATE PARALYSIS OF GAZE. The cerebral hemispheres control the direction of gaze by coordinated movements of both eyes. A supranuclear lesion therefore affects movements of both eyes together in a particular direction. Each eye when tested separately, however, shows a full range of movement. This is an excellent example of the aphorism that 'the cortex controls movements, and the lower motor neurones control individual muscles'.

Nystagmus

Nystagmus is a series of involuntary, rhythmic oscillations of one or both eyes. It may be manifest in horizontal or vertical planes or as a series of rotations of the eye about its central axis (rotatory nystagmus). The oscillations may be equal in speed and amplitude in both directions of movement (pendular nystagmus) or movement in one direction may be faster than in the other (jerking nystagmus). When there are fast and slow components, the direction of the nystagmus is arbitrarily defined by the direction of the fast component. When severe, nystagmus may be present on looking to the side opposite to the fast component—this is a measure of severity, not an indication of nystagmus to both sides. It may occur spontaneously or be induced in response to a stimulus such as rotation of the head. When testing for nystagmus it is important to keep the visual fixation point within the field of binocular vision. Some normal people show sustained fine jerking nystagmus at the extremes of lateral gaze, especially when fatigued.

Pathological nystagmus results from impairment of the mechanisms controlling conjugate eye movements, namely:

Gaze Mechanisms. Voluntary conjugate movements of the eyes depend on pathways descending from, centres in the frontal lobe to brain stem structures which then relay impulses to the nuclei of the extra-ocular muscles (Fig. 95).

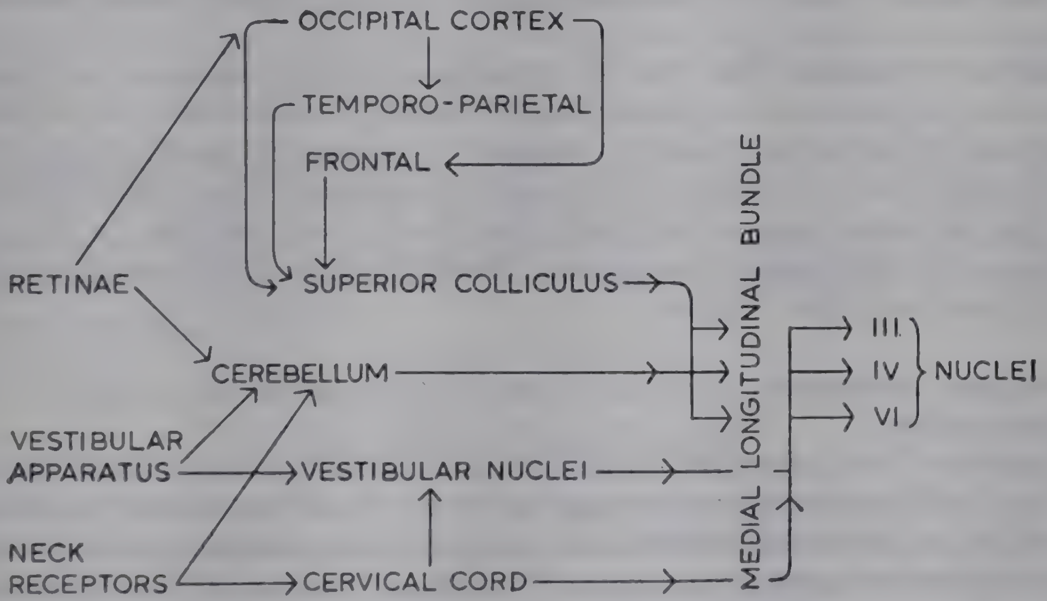


FIG. 95

DIAGRAM OF PERIPHERAL, CORTICAL, AND BRAIN STEM CONTROL OF CONJUGATE GAZE.

Fixation Mechanisms. Reflex mechanisms enable the object of interest continuously to be viewed by the macular area of each eye even when the object is moving. These reflexes are mediated through pathways which run from the eye to the cortex of the occipital lobe and adjacent parietal lobe and to the superior colliculi of the brain stem.

Vestibular Mechanisms. These are reflex adjustments which enable the retinal images to be stabilised, even when the head is being moved in space: they are evoked by impulses arising in the semicircular canals of the labyrinth and these are relayed to the central vestibular systems.

Cerebellar Mechanisms. The cerebellum also participates in the coordination of eye movements, as it does in the coordination of limb movements.

Peripheral Mechanisms. All the above mechanisms need an efficient effector apparatus and hence peripheral lesions of nerve or muscle may also lead to nystagmus.

TYPES AND CAUSES OF NYSTAGMUS

Gaze Nystagmus. This is usually due to lesions of the brain stem. The nystagmus is of jerking type. There is no nystagmus when the eyes are in the central position but it appears on deviation of the eyes laterally. The faster component is always in the direction of gaze.

A special form of gaze nystagmus involves only the abducting eye on conjugate lateral deviation of the eyes. This is called *ataxic nystagmus* and results from lesions of the medial longitudinal bundle in the pontine region. The ocular movements are dissociated. On looking to one side, the abducting eye shows coarse nystagmus. The other eye fails to adduct fully and if it exhibits nystagmus this is of smaller amplitude. This type of nystagmus is common in disseminated sclerosis but also occurs in brain stem gliomata and Wernicke's encephalopathy.

Fixation Nystagmus. This type of nystagmus is usually present when the eyes are in the mid position, i.e. gazing straight ahead. A common cause of fixation nystagmus (often called ocular nystagmus) is defective central vision, which usually gives rise to pendular movements. Congenital visual defects produce this type of nystagmus, which may also result from working in very dark environments, as in 'miner's nystagmus'. Rarely fixation nystagmus is associated with diffuse brain stem lesions.

Vestibular Nystagmus. This may arise from lesions of the labyrinth or the vestibular nerve.

Disorders of the Labyrinth. Imbalance between labyrinthine stimuli from the two ears leads to jerking movements of both eyes. If the lesion involves the end-organs in the semicircular canals or their central connections, nystagmus is precipitated by sudden movements of the head. Lesions of the otolith organs or their central connections cause nystagmus which occurs when the head is in a particular position.

Spontaneous nystagmus is present with acute lesions of the labyrinths but tends to subside in a few days or months. This tendency to adaptation may be seen during testing, as nystagmus, brought on by movement of the head or by caloric stimulation, is not maintained. It may be difficult to elicit again if the test is repeated. It is often associated with vertigo (p. 823) and this is also brief. Cochlear function is usually affected, causing tinnitus or deafness. Labyrinthine nystagmus may be caused by inflammatory diseases (serous or purulent labyrinthitis), degenerative middle ear disease, hypertension, atherosclerosis of the internal auditory artery, head injury and Ménière's syndrome.

Lesions of the Vestibular Nerve. Nystagmus due to lesions of the eighth nerve has the same features as labyrinthine nystagmus. It may be due to an acoustic neuroma or neuronitis (p. 823). The latter is a short-lasting disease.

Lesions of the Central Vestibular Systems and Cerebellum. Spontaneous nystagmus, or nystagmus induced by head position or head movement, may be found with brain stem lesions affecting the vestibular nuclei. Spontaneous nystagmus unaffected by head position and maximal on looking to the side of the lesion is found with some cerebellar lesions. Central nystagmus often occurs without vertigo, but when nystagmus is present it tends to persist and neither the nystagmus nor the vertigo shows the adaptation which is a feature of a peripheral lesion. Central nystagmus and vertigo often occur without cochlear symptoms, and may be associated with other brain stem symptoms, such as diplopia, or with asynergia of the limbs or dysarthria if the lesion involves cerebellar connections. The nature of the nystagmus may be like that of peripheral vestibular lesions, but vertical nystagmus, or nystagmus which affects each eye differently, is always central in origin. It may be caused by disseminated sclerosis, vascular lesions such as occlusion of the posterior inferior cerebellar artery, pontine and cerebellar tumours, encephalitis, syringobulbia (p. 885), or as the result of toxic states of which alcoholism is the most common. Post-concussional vertigo and nystagmus may be peripheral or central in type, and they are often precipitated by a particular posture of the head. Indirect disturbances of the vestibular nuclei may occur when the intracranial pressure is raised. Nystagmus is then a 'false localising sign'.

Nystagmus due to Muscle Paresis. This common cause of nystagmus is often overlooked. If one or more of the extra-ocular muscles are weak, then the affected eye will manifest jerking nystagmus when it is moved by the weakened muscles. Thus a partial sixth nerve palsy will result in nystagmus in the affected eye on attempted abduction.

The Fifth Cranial Nerve

The trigeminal nerve has an extensive sensory distribution through its three branches, the ophthalmic, maxillary and mandibular divisions. It supplies the skin of the face (excluding the angle of the jaw), the cornea, the sinuses, the mucous membrane of the nose, the teeth, the tympanic membrane and common sensation (but not taste) to the anterior two-thirds of the tongue. The motor division of the nerve innervates the temporal, masseter and pterygoid muscles which are responsible for the closure and opening of the jaw. The nerve fibres and nuclei may be involved within the brain stem by conditions such as syringobulbia and thrombotic lesions, and the peripheral nerve by localised pressure such as occurs in cerebral aneurysms in the region of the cavernous sinus, and by tumours of the cerebellopontine angle. The ganglion of the nerve may also be involved by herpes zoster, giving rise to the characteristic shingles lesion over the skin of the face and causing ulceration of the cornea when the ophthalmic division is involved.

Trigeminal Neuralgia (Tic Douloureux)

This is a condition of unknown aetiology and without recognised histopathology which usually affects elderly people.

Clinical Features. Pain, usually paroxysmal and of lancinating type is the characteristic feature. The pain is confined to the distribution of the fifth nerve. The maxillary or mandibular divisions of the nerve are usually first involved and spread from one to the other is common but the ophthalmic division is rarely affected. Each paroxysm lasts for only a few seconds but the stab of pain may be followed by a dull ache, or frequent attacks following one another may make the pain appear to be of longer duration. The pain is precipitated by touching localised 'trigger zones' on the affected side of the face. A cold wind blowing on the face, washing the face, chewing or even talking may be sufficient to bring on an attack. Paroxysms may continue for days or weeks, after which a remission of equal or longer duration may follow, but remissions become shorter and less frequent as the disease progresses. The agonising pain commands the patient's full attention. It may provoke a spasm of the facial muscles. No abnormalities of fifth nerve function can be detected on examination.

Diagnosis. When a typical history is volunteered by an elderly patient the diagnosis is obvious. If similar symptoms occur in a young person the possibility of disseminated sclerosis needs to be considered. Facial pain, mimicking trigeminal neuralgia may rarely be a manifestation of basilar aneurysm or cerebral tumour, particularly of a neurofibroma of the fifth nerve itself. In these and other instances when the fifth nerve is implicated in disease processes, the pain is often continuous and there are usually signs of fifth nerve dysfunction and there may be associated disturbances of other cranial nerves or neural pathways.

Treatment. Medical treatment should be used in the first instance. Carbamazepine 200 mg thrice daily is the most effective drug. Phenytoin 100 mg three times daily is also useful and may with advantage be combined with carbamazepine. Either or both of these drugs will reduce the frequency and severity of the pain in the majority of patients. Long remissions may occur. If pain persists and remissions are rare or of short duration it is necessary to interrupt the central passage of pain impulses by injection of phenol or alcohol into a branch of the nerve, if neuralgia is localised, or into the Gasserian ganglion. Section of the sensory part of the fifth nerve or its descending root in the medulla has the disadvantage of requiring intracranial operation but permits sparing of corneal sensation which is difficult to achieve with injection of the ganglion. These procedures secure permanent relief from pain but the face becomes anaesthetic. Loss of sensibility from the cornea demands that special care must be taken to avoid trauma with its danger of subsequent corneal ulceration.

Prognosis. Remissions are common in the early years but spontaneous recovery is rare. The attacks tend to become more frequent and of longer duration.

The Seventh Cranial Nerve

The facial nerve innervates the muscles of expression of the face and, through its chorda tympani branch, carries taste fibres from the anterior two-thirds of the tongue. Paralysis of the facial muscles may be due to:

(1) lesion of the fibres of the upper motor neurones concerned with voluntary movement, (2) lesion of the fibres of the upper motor neurones concerned with emotional movement, (3) lesion of the lower motor neurones.

1. Upper motor neurone fibres originating in the lower part of the pre-central gyrus are distributed to the part of the opposite facial nucleus subserving the muscles of the lower part of the face, and to the parts of the facial nuclei on both sides of the pons which supply the upper parts of the face. Accordingly, a lesion of the upper motor neurones affects more severely the voluntary movement of the lower part of the face, contralaterally. Weakness of the upper part (the orbicularis oculi and frontalis muscles) may occur transiently but is often absent because the lower motor neurones to the upper facial muscles are supplied by upper motor neurones from both hemispheres. The patient is unable to retract the angle of the mouth on command, but in smiling and talking the mouth may move well because emotional movement is controlled by upper motor neurones which are not those concerned with voluntary movement of the face.

2. Upper motor neurones concerned with emotional movement of the face take origin further forward in the frontal lobe and so may be damaged by a lesion which spares the fibres for voluntary movement of the face. Involvement of these fibres is revealed by defective movement of the angle of the mouth when the patient smiles and talks, with preservation of the ability to retract the angle of the mouth on command.

3. Since the lower motor neurone is the final common pathway, complete damage to the facial nucleus or nerve abolishes both voluntary and emotional movements equally in upper and lower parts of the face. Lower motor neurone paralysis restricted to part of the facial muscles can occur only when the lesion is distal to the branching of the nerve, e.g. with disease of the parotid gland, through which the nerve passes, or in leprosy.

When the lesion is at the level of the geniculate ganglion, the patient may complain that sounds seem too loud (the hyperacusis is due to paralysis of the stapedius muscle) and there is loss of taste sensation on the anterior two-thirds of the tongue (chorda tympani).

The most common cause of damage to the nerve proximal to its branching in the parotid gland is Bell's palsy but it may be damaged by disease of the brain stem, by an acoustic neuroma, or by inflammation during its passage through the middle ear.

Bell's Palsy

Aetiology. This condition occurs in both sexes at any age. The cause is unknown but is believed to be an inflammatory lesion in the stylomastoid canal, the paralysis being due to compression of the nerve fibres by oedema.

Clinical Features. There may first be a slight aching pain behind the ear for one or two days then unilateral facial paralysis rapidly develops, but pain may be absent. The eye on the affected side cannot be closed and may water. The mouth is drawn over to the opposite side (so that it may appear to the patient to be due to spasm of the normal side), saliva or fluids may run from the angle of the mouth and, during chewing, food may collect between the teeth and the paralysed cheek. The patient often complains that the affected side feels 'numb', as if injected with a local anaesthetic, but there is no objective loss of sensation of the skin. On examination there is paralysis of the upper as well as the lower part of the affected side of the face. The lines of expression are flattened out on the weak side and the patient is unable to wrinkle his brow, whistle or retract the angle of his mouth. He cannot close the eye and on attempting to do so the eyeball rolls up. The nerve to the stapedius muscle and the chorda tympani respectively leave and join the main trunk before it leaves the stylomastoid foramen so signs of affection of these two nerves are absent in most cases of Bell's palsy.

Diagnosis. The differential diagnosis of facial palsy due to lesions of the upper and lower motor neurones is discussed above (p. 821).

Herpes zoster of the geniculate ganglion is a rare cause of facial palsy which is accompanied by vesicular eruptions on the anterior two-thirds of the tongue or in the ear.

Treatment. It is usually sufficient to give aspirin if the ear is painful and to protect the ear from cold but corticosteroids may reduce inflammation and oedema during the first 48 hours after the onset. A splint may be fitted to prevent over-stretching of the angle of the mouth. When voluntary movement begins to return, active facial exercises in front of a mirror should be practised several times a day. Surgical decompression is not recommended. Electrical stimulation does not hasten recovery and may lead to secondary contractures. When recovery does not occur, a nerve anastomosis or a plastic operation should be considered.

Prognosis. Recovery usually starts in three to four weeks and is complete in three to six months but it is sometimes delayed or incomplete. Unfortunately it is difficult to recognise cases with a poor prognosis at a time when surgical treatment might be considered. Recovery is probable if any voluntary contraction of any paralysed muscle can be seen within a month, and the presence of a normal intensity-duration curve on electrical stimulation after the first week is strong evidence that the nerve has not degenerated. Recovery is unlikely if the intensity-duration curve is of the denervation type. Regeneration of the nerve is possible but the cosmetic result may be marred by the presence of inappropriate movements such as closure of the eye when it is intended to move the lips, due to random regeneration of fibres to the wrong muscles. Recurrence of facial palsy on either side is exceptional but some individuals appear to be unduly susceptible.

The Eighth Cranial Nerve

The auditory nerve has two components, the cochlear nerve which is concerned with hearing and the vestibular nerve which is concerned with the appreciation of the position of the head and its movement in space. It is impossible without special tests to differentiate lesions involving these nerves from lesions confined to their end-organs in the inner ear. Irritative lesions of the inner ear or of the cochlear nerve cause tinnitus, and destructive lesions deafness. Thus, tinnitus may be an early symptom of a neuroma of the eighth nerve (acoustic neuroma) but it is often due to aural causes. The most important destructive lesion of the eighth nerve is an acoustic neuroma, but it may also be damaged in meningitis, and by the toxic effects of streptomycin and kanamycin.

Irritative lesions of the vestibular part of the eighth nerve cause vertigo.

Vertigo

The term 'vertigo' is used by many people to describe a sensation of 'giddiness' or 'dizziness'; these symptoms are common in patients with an anxiety neurosis or with transient general upsets of cerebral function as well as in lesions of the vestibular pathways. For this reason it is convenient to restrict the term 'vertigo' to the description of a subjective feeling of movement of the external environment or of the brain within the head. The movement may be rotatory or a feeling of displacement in one direction. Vertigo is always accompanied by a disturbance of balance which usually causes the patient to seek support, and if sudden and severe may throw him to the ground. It often causes a reflex autonomic discharge leading to cold sweating, pallor, nausea, vomiting, and sometimes diarrhoea, bradycardia or even syncope.

The most important causes of vertigo are:

Cerebellar Lesions. Cerebellar lesions may cause vertigo when the cerebello-vestibular connections are involved but this symptom is not invariable.

Brain-stem Lesions. Lesions such as insufficiency of the basilar artery, medullary infarction or syringobulbia may cause severe vertigo when they involve the vestibular nuclei. The vertigo may be produced by particular positions of the head.

Lesions of the Vestibular Nerve. An acoustic neuroma may damage the nerve and cause vertigo. Vestibular neuronitis is a more common cause; it is a benign short-lasting condition of unknown aetiology which may occur in epidemics.

Aural Lesions. Aural lesions of many kinds, including otitis media and Ménière's syndrome, cause vertigo. The labyrinth may be damaged in a head injury and the vertigo may then be most severe when the head is in a certain position, usually backwards and to one side. A similar type of positional vertigo may occur in brief paroxysms. It is a benign condition which may disappear after a few months. The labyrinth may be damaged by mumps and by various toxic drugs such as streptomycin. Quinine and salicylates are also believed to cause vertigo by an action on the middle or inner ear. Hearing is almost invariably affected when the lesion is labyrinthine rather than in the nerve or central connections.

Ocular Lesions. Diplopia may be accompanied by vertigo because the false projection of one image causes confusion regarding position in space.

Ménière's Syndrome

Ménière's syndrome is characterised by recurrent paroxysms of vertigo associated with tinnitus and progressive nerve deafness.

Aetiology. The cause is unknown, but the condition is associated with dilatation of the endolymphatic system (hydrops) due to increase in the amount of endolymph. Many patients also give a history of migraine.

Clinical Features. The most common initial symptoms are progressive deafness and tinnitus which are frequently slight at the onset. Sooner or later vertigo occurs and is characterised by suddenness of onset and severity. It may develop so suddenly that the patient may fall, and at the height of the attack he may be unable to stand. There is often accompanying nausea and vomiting, and there may be sweating, weakness and faintness. Deafness and tinnitus may be intensified during the attack which may last for a few minutes to several hours. Examination during an attack shows rotatory nystagmus and ataxia. Between attacks there is only nerve deafness with impaired vestibular function as shown by caloric tests.

Diagnosis. The paroxysmal nature of the attacks, and the association with tinnitus and nerve deafness are characteristic. Other causes of vertigo are excluded by careful examination.

Treatment. No treatment will abort an episode of vertigo; during severe attacks the patient should lie still and may be helped by an intramuscular injection of 50 mg of chlorpromazine. Treatment is aimed at preventing or reducing the number of attacks. Phenobarbitone (30 mg t.d.s.), prochlorperazine (5 mg t.d.s.), betahistidine (8 mg t.d.s.), and others are used for this purpose. All of these drugs are sometimes effective but none is consistently so. If attacks are frequent and disabling, destruction of the labyrinth by surgery or ultrasonics may be required.

Prognosis. The frequency of attacks tends to decrease as deafness increases but the disease may last many years.

The Ninth, Tenth and Eleventh Cranial Nerves

These nerves are grouped together because isolated lesions of one nerve alone are rarely encountered. The glossopharyngeal nerve (IX) transmits taste and common sensation from the posterior one-third of the tongue and motor fibres to the pharynx; the vagus nerve (X) is the parasympathetic nerve for the viscera of the thorax and upper part of the abdomen and also supplies somatic motor fibres to the soft palate and the larynx; the spinal accessory nerve (XI) supplies the trapezius and sternomastoid muscles. Unilateral lesions disturb their somatic functions but do not appreciably affect visceral function. These nerves or their nuclei may be involved by disease of the medulla such as syringobulbia or in their course across the posterior fossa by neoplasms and basal meningitis. Lesions at the jugular foramen, such as thrombophlebitis of the internal jugular vein following suppuration in the skull or neck, may involve all three nerves as they emerge from the skull.

The Twelfth Cranial Nerve

The hypoglossal nerve supplies motor fibres to the muscles of one side of the tongue. Upper motor neurone lesions cause spastic contraction of the muscle fibres. The tongue is small and pointed but not atrophic. Articulation is defective (spastic dysarthria) especially for the lingual sounds. There is rapid recovery of function after a unilateral lesion of upper motor neurone type, but bilateral lesions cause permanent dysarthria. This may occur in motor neurone disease (p. 881) or in pseudobulbar palsy due to bilateral impairment of blood supply in the internal capsules (p. 843). Lower motor neurone lesions cause wasting and fibrillation of the affected part of the tongue and, when protruded, the tongue deviates to the side of the lesion. The usual cause is motor neurone disease.

The lower cranial nerves may be involved by carcinoma of the nasopharynx spreading to the base of the skull so otolaryngological examination is necessary. All cranial nerves, but particularly those emerging from the base of the skull, may be affected by bone disease in that area, particularly by Paget's disease.

The Cervical Sympathetic Fibres

The higher centres for autonomic functions in the hypothalamus are connected with some areas of the cortex, notably the orbital surface of the frontal lobe and the insula. From the hypothalamus sympathetic fibres descend through the brain stem and spinal cord to their lower neurones in the small lateral horn of the thoracic region of the spinal cord from which they pass into the anterior spinal roots from T_1 to L_2. White rami communicantes leave these roots and convey the fibres to the paravertebral sympathetic chain where a relay occurs either immediately or after rising or descending to a ganglion more remote in the chain. Grey rami communicantes then go to peripheral sympathetic plexuses which supply the principal viscera; others rejoin the spinal nerves and are distributed with them to some of the blood vessels and glands in the territory of those nerves. Those destined for the head and neck emerge mainly through the first thoracic anterior root, and ascend in the cervical sympathetic chain, reaching their final destination by means of the plexuses in the walls of blood vessels. Stimulation of the cervical sympathetic fibres causes dilatation of the pupil, protrusion of the eye-ball and elevation of the upper eyelid; conversely paralysis of these fibres results in pupillary constriction, enophthalmos and ptosis (*Horner's syndrome*). In addition, sweating is impaired on that side of the face. These signs may occur in lesions of the brain stem as syringobulbia and thrombosis of the posterior inferior cerebellar artery, in lesions of the cervical part of the spinal cord such as syringomyelia, and in conditions at the thoracic outlet such as bronchial carcinoma at the apex of the lung (p. 402).

COMA

The state of consciousness is associated with cortical activity activated by impulses from the thalamus and mid-brain. The reticular formation receives collateral axons from the main spinothalamic and special sensory pathways and from the cortex and sends fibres to the cortex which it alerts. The lower part of the reticular formation projects to the spinal cord for regulation of muscle tone (p. 799). Disorders of the cortical or brain-stem poles of this system, but particularly the latter, are associated with disturbance of consciousness.

Impairment of consciousness can be subdivided into arbitrary stages of drowsiness, stupor and coma; it can be graded according to the type of stimulus required to cause arousal (p. 953). In the same way coma can be arbitrarily graded according to the degree of loss of reflex activity. The 'vital' reflexes of coughing, respiration and vasomotor control are the last to disappear with deepening coma and the patient must be protected from the consequences of their loss.

Aetiology. The principal causes of coma are:

PAROXYSMAL LOSS OF CONSCIOUSNESS. Sudden brief loss of consciousness with full recovery but often with recurrences may be found in epilepsy (p. 827), Adam-Stokes attacks (p. 238) and syncope (p. 241).

CEREBRAL DISORDERS. *Head Injury*. There is a history of trauma and there may be signs of external injury. In concussion the face is pale, reflexes diminished or absent, and pupils equal, dilated and sluggish. If there is compression due to intracranial haemorrhage the face may be flushed, breathing is stertorous and the reflexes may be asymmetrical. The pupil on the injured side first contracts and then dilates and the other pupil subsequently reacts similarly. It is well to remember that a patient becoming unconscious or incapable for some reason other than trauma may fall and injure his skull.

Cerebrovascular Accidents (p. 842). Apoplexy is usually of sudden onset if it causes loss of consciousness. There are signs of a focal cerebral lesion such as a hemiplegia, and of meningism if subarachnoid bleeding has occurred. There may also be evidence of the cause such as hypertension, atherosclerosis, or a cardiac disorder associated with embolism.

Meningitis (p. 855). Coma is of gradual onset in most types, being preceded by meningeal irritation and fever but in meningococcal meningitis these signs may have been present for only a few hours. The cerebrospinal fluid is turbid and contains polymorphonuclear leucocytes.

Encephalitis (p. 864). Viral encephalitis as a cause of coma is rare. It is important to bear in mind cerebral malaria in the tropics or in any comatose patient who has recently returned from a country in which malaria is prevalent. Early treatment is completely effective (p. 967). Coma also occurs in African trypanosomiasis, but is a late complication (p. 974).

Cerebral Tumour and other causes of raised intracranial pressure. As pressure rises the brain stem becomes displaced and ischaemic. Consciousness is lost slowly and signs of pressure coning and papilloedema develop (p. 833).

ABNORMAL METABOLIC STATES. *Hypothermia*. Coma is associated with body temperature lower than 30° C. Hypothermia may be due to exposure to severe climatic conditions or from normal loss of body heat if a poorly clad person lies helpless or unconscious in an unheated room for one or more days especially if he is an infant or elderly and thin. It may be a serious complication in cases of self-poisoning (p. 853). Hypothermic coma may occur in the absence of cold if the metabolic rate is depressed by myxoedema (p. 643) or hypopituitarism (p. 628).

Heat Hyperpyrexia. There is a history of heat exposure, a high body temperature and a striking absence of sweating.

Diabetic Keto-Acidosis and Hypoglycaemia (pp. 698 and 697).

Renal Failure (p. 598).

Hepatic Failure (p. 560).

Hypercapnia (p. 323).

POISONING. The manifestations and treatment of poisoning are discussed on pages 950-959.

Differential Diagnosis. Coma may be difficult to differentiate from some psychotic conditions, e.g. depression or from akinetic mutism in which the patient lies in a stuporous state unresponsive to most stimuli. If he is watched continuously it is seen that the non-comatose patient is not wholly out of touch with his surroundings and his vital reflexes remain intact. Physical examination is negative and a history of psychological abnormality can usually be obtained from a relative or friend. Akinetic mutism may be found in some disorders of the region of the third ventricle but will be associated with signs of cerebral damage.

Management of Coma. The unconscious patient is exposed to special hazards as he is dependent on reflexes to protect his body and maintain respiratory and cardiovascular function and the reflexes are progressively lost as coma deepens. Until full consciousness returns the patient must be protected from these hazards in addition to those of the causative disease. The problems are discussed further on pages 847 and 951.

THE EPILEPSIES

An epileptic fit may be defined as a brief disorder of cerebral function, usually associated with a disturbance of consciousness, and accompanied by a sudden, excessive, electrical discharge of cerebral neurones. The electrical activity recorded by the electro-encephalogram (EEG) is of high voltage relative to the background and results from a synchronous discharge of neurones. The cause of this is not fully understood but it seems likely that inhibitory neural systems normally prevent its development. It may be that many of the presently unknown causes of epilepsy will be found to have a biochemical basis.

There are many varieties of epilepsy, some delineated by clinical and others by electrical characteristics. They may be classified into two broad groups:

(*a*) Generalised seizures with loss of consciousness which are accompanied by generalised, symmetrically synchronous EEG discharges and which originate from deep, central mid-line structures.

(*b*) Partial or focal fits in which consciousness may be retained. The discharge originates in a localised area of brain and may or may not thereafter spread diffusely.

Generalised Epilepsy

There are two common varieties of generalised fit—grand mal and petit mal.

Grand Mal. These fits conform to a stereotyped clinical pattern in which several stages may be recognised:

1. A *prodromal phase*, lasting hours or days, may warn the patient that an attack is impending. This is an occasional phenomenon and usually takes the form of a change of mood.
2. An *aura*, which is uncommon in grand mal fits. When it does occur, it is of brief duration and vague nature, usually being no more than an apprehension that a fit is about to occur.
3. The *tonic stage*, which is an invariable part of a grand mal attack. At the onset of this stage the patient loses consciousness and, if upright, falls to the ground. A sustained, tonic spasm of all the musculature occurs and involves the respiratory muscles, so that air is forcibly expired through the partially closed glottis giving rise to a sound or 'cry'. This phase lasts 20 to 30 seconds and during this time respiratory movements are suspended so that cyanosis occurs.
4. A *clonic phase* in which the sustained tonic spasm gives place to interrupted powerful jerking movements of face, body and limbs. The movements of jaw and tongue cause saliva to froth in the mouth. This stage, also, lasts about half a minute.
5. The *stage of relaxation:* After movements cease, the patient lies in a flaccid, comatose state which evolves into normal sleep. This phase often lasts only a few minutes but may be prolonged for half an hour or more.

During the tonic and clonic stages the patient may bite and chew his tongue and may be incontinent of urine and, less often, of faeces. After regaining consciousness there is often a phase of variable duration wherein the patient is confused and may suffer from headache.

Petit Mal. This term is often used imprecisely. It is best restricted to those cases showing a characteristic EEG pattern, namely bilaterally synchronous spike and slow wave complexes occurring at a frequency of three per second. This pattern occurs with three types of clinical manifestation:

1. The most common variety of attack takes the form of a transient loss of consciousness. The patient interrupts whatever he is engaged in and may stare blankly ahead. The whole episode usually lasts only 10 or 15 seconds, and is so brief and undramatic that it may pass unnoticed. Such 'absences' as they are called, may occur very frequently in childhood. Petit mal invariably starts in childhood but may persist into adult life. Sometimes the attacks cease during adolescence or give place to grand mal fits.
2. Less commonly the brief loss of consciousness is accompanied by myoclonic jerking of the arms.
3. The least common type of attack is the akinetic seizure in which the patient falls to the ground unconscious but recovers consciousness, and is able to rise again, almost immediately.

Partial or Focal Epilepsy

Since there are many neuronal regions from which epileptic discharges may originate there are many clinical variations of focal fits. Any focal discharge may spread to become generalised, and initially localised clinical disturbances may progress to mimic a grand mal fit. It is important, therefore, to establish the nature of the phenomena which occur at the onset of any form of seizure since these indicate the focal origin.

1. The *temporal lobe* is the commonest site of focal epilepsy. Most characteristic of the clinical manifestation are hallucinations of smell though these are uncommon; hallucinations of taste, hearing or sight also occur. Also indicative of temporal lobe fits are disturbances of memory including the so called *déjà vu* phenomenon. This refers to the patient's sensation of reliving an experience or a feeling of great familiarity with his environment. Sometimes these features are associated with intense emotional or mood changes.

In temporal lobe attacks consciousness is usually disturbed but not necessarily lost. The patient often maintains some contact with his surroundings but feels remote from them, often likening the experience to a dream-like state. Occasionally the patient during this state will carry out well-coordinated and apparently purposeful motor acts, even of a violent or antisocial nature, without any memory of such activity thereafter.

Temporal lobe discharges do not always give rise to such distinctive clinical features and an EEG may be required in order to reveal the temporal lobe origin of seizures.

2. *Jacksonian epilepsy* is a term best restricted to fits in which clinical disturbance of function, initially confined to a circumscribed part of the body, spreads to involve adjacent areas. There is a relatively slow 'march' of clinical events which reflects the spread of the electrical discharge to nearby cortical areas. Motor seizures usually take the form of involuntary twitching or clonic movements which begin in part of a limb, spread to involve the whole limb, then perhaps the whole of one side of the body or the involvement may even eventually become bilateral. The extent of the spread is highly variable. Consciousness may or may not be lost. Sometimes after recovery from a Jacksonian fit, the parts affected remain paralysed. This is called a Todd's palsy and if prolonged for more than an hour or two suggests that there is a structural lesion in or near the cortical representation of the paralysed part.

Causes of Epilepsy. In many, perhaps the majority, of cases, epilepsy arises from causes which at present cannot be identified. This large category of cryptogenic or idiopathic epilepsy includes many cases in which generalised fits first occur in children whose relatives are similarly affected but also includes many other cases without a family history or with atypical fits.

Any intracranial disease may give rise to epilepsy, either as a manifestation of an active pathological process or as a sequel thereof. Important causes of 'symptomatic' epilepsy include cerebral tumours, head injuries and cerebrovascular disease.

Fits may occur as a result of disease elsewhere than in the brain. Hypoglycaemia, uraemia, heart block, ingestion or sudden withdrawal of alcohol or drugs are but a few of the conditions which may evoke seizures.

Clinical Approach. The first step is to make a diagnosis of epilepsy. This is essentially a clinical process. Observation of an episode by a trained observer is the best and most certain method of diagnosis, but is rarely possible. A good description by, and cross-examination of, an eyewitness furnishes useful, and often conclusive evidence. The patient's own account of his attacks and the circumstances attendant upon them will sometimes give diagnostic information. The EEG is not a substitute for this type of clinical assessment nor can an EEG, recorded between attacks, alone establish or refute a diagnosis of epilepsy. The EEG may be helpful in supporting a clinical diagnosis and may be of great value in localising a cerebral cause of symptomatic epilepsy.

Note should be made of factors which precipitate attacks. Some patients have fits only during sleep, or when they are pyrexial. Others recognise that certain sensory stimuli, such as flickering light, or emotional disturbances trigger their seizures. A careful aud detailed history, including past illnesses and family history, is the key to effective management of patients suffering from epilepsy.

After the diagnosis of epilepsy has been established the next stage is to assess its cause. In practice the most important aspect of this process is to recognise patients whose epilepsy is due to a structural or progressive lesion.

Fits of recent onset, of focal nature, occurring in patients of middle age, would obviously suggest an underlying lesion, perhaps a tumour. Accompanying headache and neurological signs would strengthen such a suspicion.

The history and examination will in most cases furnish pointers to the aetiology of fits and hence to the need for special investigations. An EEG and skull X-rays should be obtained in all cases. Before embarking on more traumatic investigations, such as lumbar puncture or contrast radiography (p. 836) the need for such tests should be appraised in the light of the clinical features. In many instances repeated observation of patients over a period is the most valuable and least distressing course of action.

Treatment. The cause of epileptic fits should, if possible, be treated. In rare instances treatment can be curative, as for example, by surgical removal of an insulin-secreting adenoma in patients whose fits are due to hypoglycaemic episodes. Benign cerebral tumours obviously need surgical removal though even successful surgery does not necessarily abolish fits.

In the vast majority of cases treatment is designed to ameliorate the effects of fits by reducing their number and by adjustment of the patient's circumstances. Patients with epilepsy should lead as normal a life as possible. Children should continue their education and adults should pursue their employment, avoiding obviously hazardous jobs and hobbies.

Precipitating factors should be avoided if this be feasible. Patients whose fits are consistently evoked by flickering light should avoid stimulation of this kind.

Anticonvulsant drugs will in most cases be needed to control fits. For all forms of epilepsy, phenobarbitone, given in doses of 30 mg b.d. to 60 mg t.d.s. is useful. Phenytoin (100 mg t.d.s.) and primidone (250 mg t.d.s.) are of value in the treatment of grand mal fits. Phenytoin may, with advantage, be combined with either phenobarbitone or primidone and any of these three drugs may also be used to treat focal attacks. Drowsiness may occur with all of these drugs; primidone and phenytoin may give rise to megaloblastic anaemia and phenytoin may cause cerebellar ataxia or hypertrophic gingivitis. Long-continued administration of these drugs may cause osteomalacia (p. 142).

The most effective drug for the treatment of petit mal is ethosuximide (250-500 mg t.d.s.); troxidone (300 mg t.d.s.) is also helpful.

There are numerous other anticonvulsant preparations which can be used as supplements or substitutes for the above drugs. For grand mal fits mesontoin, carbamazepine and diazepam are useful. Patients suffering from petit mal may be helped by phensuximide or acetazolamide and sulthiame is worth trying in cases of temporal lobe epilepsy.

It is essential that patients on anticonvulsants should regularly be reviewed and their treatment tailored to their individual needs. An anticonvulsant drug should not be discontinued abruptly as status epilepticus may be precipitated.

Status epilepticus refers to a continuous succession of fits occurring without any period of recovery. It may be fatal if not rapidly controlled. It is more common in childhood or in epilepsy associated with intracranial lesions but may occur in all types of epilepsy if medication is irregular or is suddenly withdrawn.

Treatment should be prompt and energetic since status epilepticus constitutes a grave emergency. An adequate airway and respiration must be maintained and the fits suppressed. Sodium phenobarbitone 200 mg given intramuscularly at two-hourly intervals or phenytoin 250 mg intramuscularly at intervals of four hours or paraldehyde 10 ml intramuscularly followed by 6 ml every half-hour, are all sometimes effective.

In severe cases and in those in which intramuscular treatment has been ineffective, intravenous therapy is required. Two preparations are used. As much as 100 mg of thiopentone or 60 mg of diazepam are slowly injected until fits cease and the corresponding drug is then given by slow intravenous drip for as long as necessary. Both of these drugs are highly effective but should be used in this way only when means of artificial respiration are available.

Narcolepsy

This is characterised by irresistible attacks of sleep from which, however, the patient can be aroused immediately. He may go to sleep at work and several attacks may occur in a day. It is often associated with three other phenomena; *cataplexy*, in which, as a result of a sudden emotion, power is lost from the limbs, though consciousness is preserved; *sleep paralysis*, in which on waking or falling asleep the patient finds himself unable to move though mentally he is wide awake; *hallucinatory states*, in which vivid and terrifying hallucinations occur, often just as the patient is falling asleep. This combination of symptoms may be associated with disease in the region of the hypothalamus. In other cases no abnormality can be demonstrated in the nervous system. Amphetamine sulphate 5-10 mg two to four times a day, or one 15 mg spansule in the morning is of value in reducing the frequency of attacks.

CEREBRAL TUMOURS

Intracranial tumours account for 2 per cent of deaths at all ages. Neoplasms classified histologically as malignant and benign occur but the implications of these categories differ from those in other sites. Since they grow within the rigid confines of the skull all types of neoplasm may cause disability and death by impinging on and displacing the cranial contents. The clinical features produced by an intracranial tumour depend primarily on its site of origin and its rate of growth. The histological characteristics of tumours offer a guide to rapidity of growth and to the possibility of complete removal.

Pathology. Malignant cerebral tumours rarely give rise to extracerebral metastases but approximately a half of all brain tumours are secondary deposits from carcinoma elsewhere, particularly in bronchus and breast.

Of primary cerebral tumours those derived from glial cells are the commonest. These vary in cellular type, in degrees of malignancy and in rates of growth. An astrocytoma Grade 1 is a slow-growing, infiltrative tumour which may spread widely throughout the brain, sometimes for years, before causing serious disability. A Grade 4 astrocytoma (also called a glioblastoma multiforme) is a highly malignant, fast-growing tumour causing rapid clinical deterioration. Other glial tumours such as oligodendroglioma and ependymoma are graded from 1 to 4 as the degree of malignancy increases. Medulloblastoma occurs most commonly in children, arises usually in the cerebellar vermis, and is almost always highly malignant. The various types of glioma account for a quarter of all cerebral tumours. They can rarely be completely excised.

Meningiomas comprise approximately one-fifth of intracranial tumours. They are almost always benign, encapsulated, attached to the dura and, in the majority of instances, completely removable. Their common sites of origin are the convexities of the hemispheres, the sphenoidal ridges, the suprasellar region and the olfactory groove.

Other less common tumours arise within the cranial cavity. Craniopharyngiomas (p. 625), adenomas of the pituitary gland and neuromas from the sheaths of the eighth and fifth cranial nerves are benign and potentially curable.

Intraventricular tumours are rare but colloid cysts of the third ventricle and papillomas of the choroid plexus can cause raised intracranial pressure and are removable.

Clinical Features. Primary brain tumours occur at all ages with a maximal incidence in the fifth decade. Medulloblastomas are commonest in children. Acoustic neuromas usually present in the third and fourth decades. Glioblastomas and meningiomas are commonest in middle life. In general brain tumours in children are situated in the posterior fossa and in those over thirty, supratentorial tumours account for 85 per cent of cerebral neoplasms.

Cerebral tumours produce symptoms and signs by their local effects and by causing alterations in intracranial pressure and hydrodynamics.

FEATURES DUE TO LOCAL INVOLVEMENT. The local effects of a tumour on adjacent cerebral tissue may cause paralysis of function and/or excitatory effects. The neural deficits produced by a brain neoplasm are dependent on the site of origin of the tumour. Lesions in the various lobes of the brain can cause the types of dysfunction outlined on pages 808-810. Vascular lesions affecting these same structures cause similar disturbances but those produced by tumours are characterised by the time course of their development. In general the focal disabilities produced by a tumour are of slow onset and are progressive. The rate of this progression is highly variable and depends on the rate of growth of the tumour and its nearness to neural structures whose interruption evokes clinical signs. Occasionally localised oedema in the brain tissue surrounding a tumour will cause a rapid progression of paralytic symptoms and the picture thus produced may mimic a cerebrovascular lesion. Sometimes, too, the initial manifestations of a metastatic tumour are of sudden onset, followed by a period of improvement. Rarely, haemorrhage into a tumour causes an acute presentation of signs and symptoms which resembles a stroke.

In addition to local paralytic effects the infiltration by tumour cells of an area of cerebral cortex often evokes excitatory responses in neighbouring cerebral neurones. Thus a discharging epileptic focus may be a manifestation of a cerebral tumour. The nature of the fit produced is variable and depends on the site of origin of the epileptic discharge and the extent of its propagation. Focal epilepsy beginning in adult life should always suggest the possibility of a tumour.

Headache is a common, but not invariable manifestation of cerebral tumour. The tumour mass tends to distort and exert traction on nearby arteries, venous sinuses or meninges which are pain sensitive structures. Headache is often localised to one area of the cranium and its site offers a rough guide to the location of the tumour. In general headache is felt on the same side as the neoplasm. Tumours which lie in the anterior and middle cranial fossae are often attended by headaches situated in front of a line joining the ears. Posterior fossa tumours usually cause headaches which are felt over the occiput or nuchal area. There are many exceptions to these generalisations.

FEATURES DUE TO INCREASED INTRACRANIAL PRESSURE. Since cerebral tumours occupy space within the rigid skull they may cause an increase in pressure within the cranium. The liability of tumours to do this varies and several mechanisms may be involved. The mass of the tumour itself, if large enough, will cause a rise in pressure due to the relative incompressibility of the brain. Slowly growing tumours may achieve large size before there is any rise in pressure whereas a highly malignant and rapidly growing tumour, though relatively small, may cause early changes. Raised intracranial pressure may also result from obstruction to the flow of cerebrospinal fluid. Subtentorial tumours are particularly liable to do this but even supratentorial lesions may cause obstruction to the foramina of Monro and tumours of the temporal lobe may compress the third ventricle. Tumours lying within the ventricles themselves may cause a sudden rise in intracranial pressure in the absence of focal neurological abnormalities.

Increased pressure may also occur as a result of cerebral oedema or from obstruction of the cerebral venous system by malignant tissue impairing the absorption of CSF. Whichever of these mechanisms is operative the end result is a rise in pressure within the skull causing similar clinical features.

Headache is an almost invariable accompaniment of increased intracranial pressure; the pain is felt diffusely over the head and is aggravated by manoeuvres which cause a further rise in intracranial pressure. The headache is intensified by bending, coughing and straining at stool. Such headaches often tend to be particularly troublesome on waking in the morning when the patient is lying flat and to be relieved to some extent when the patient stands upright and moves about since this causes a slight fall in intracranial pressure.

There is often clouding of consciousness, varying in degree from listlessness and drowsiness to deep coma, depending both on the level of the raised pressure and the rapidity of its attainment. During the early stages of this alteration in consciousness there may be behavioural and personality changes with apathy and irritability or withdrawal and inattention predominating.

Generalised epileptic fits are commonly produced by raised intracranial pressure from tumours at any site.

Many patients with increased intracranial pressure complain of dizziness which may take the form of true rotatory vertigo or of sensations of light headedness or unsteadiness. Such feelings of instability are often produced or aggravated by head movement.

Papilloedema is one of the most significant signs of raised intracranial pressure (p. 814). It may be of insidious onset and slow progression but equally often a sudden rise in pressure due to cerebral oedema or obstructive hydrocephalus causes the rapid development of papilloedema attended by haemorrhages radiating out from the optic disc. The amount of visual disturbance produced by papilloedema is variable. Often there is little change in the visual acuity but the production of transient blurring of vision when the patient stoops or bends is characteristic. Swelling of the optic nerve head is usually bilateral but may be unilateral in the early stages. When the underlying lesion has caused optic atrophy in one eye papilloedema occurs only in the other eye. Such is the case sometimes with tumours of the inferior surface of a frontal lobe which compress the adjacent optic nerve causing optic atrophy and as the tumour grows in size raised intracranial pressure supervenes and papilloedema occurs in the other eye; this is known as the Foster Kennedy syndrome.

As intracranial pressure continues to rise vomiting occurs and the pulse rate is progressively slowed.

The rise in intracranial pressure does not necessarily occur evenly over the whole of the cerebral contents and sudden alterations in pressure relationships within the skull may lead to displacement of parts of the brain. Large supratentorial lesions may cause herniation of the hippocampal gyrus and the upper brain stem downwards through the incisura of the tentorium. This not only causes damage to the hippocampal gyrus itself but may also lead to compression of the cerebral peduncles, occlusion of the posterior cerebral artery and stretching of cranial nerves, particularly the sixth nerve.

These developments themselves cause signs which may lead to erroneous localisation of the cerebral tumour. They are called false localising signs.

Commonest of these is a sixth nerve palsy occurring on the side of the lesion or bilaterally. The third nerve may similarly be involved and occasionally the fourth nerve is also implicated. The cerebral peduncle on the side opposite the tumour mass may be compressed giving rise to pyramidal tract signs on the side of the lesion. Compression of the posterior cerebral artery may lead to a homonymous hemianopia or quadrantanopia. Very rapid downward movement of the brain stem may lead to haemorrhage in the mid brain with coma and death.

Another form of herniation or 'pressure cone' is the downward movement of the cerebellar tonsils so that they impact within the foramen magnum thus compressing the medulla. This may lead to further aggravation of raised intracranial pressure since the onward passage of cerebrospinal fluid into the spinal subarachnoid space is blocked. Such an event is often manifest by loss of consciousness and the rapid development of palsies of the sixth and third nerves with dilatation of the pupil on the side of the lesion being followed by dilatation on the opposite side. Frequently when a medullary pressure cone has occurred the patient takes up a decerebrate posture, at first intermittently. These developments almost invariably lead to death.

Such brain displacements and pressure cones may occur spontaneously because of increased cerebral oedema or some other alteration in cerebral haemodynamics caused by the tumour's growth but are particularly liable to be produced if the closed CSF system is disturbed by lumbar puncture.

Methods of Investigation

The investigation of cerebral tumours should, in most instances, begin with simple and non-traumatic procedures which sometimes may obviate the need for more specialised techniques. They often will indicate which of the more sophisticated tests would be the most apposite in a particular case.

RADIOLOGY. A chest radiograph may reveal a bronchial carcinoma and hence enable the metastatic nature of a cerebral tumour to be inferred.

A straight X-ray of skull will rarely give definitive information about cerebral tumours but should never be omitted since occasionally it will reveal very significant abnormalities. Some slow growing tumours in the brain calcify and hence are visible on a radiograph of the skull. Erosion or thickening of the skull bones may point to an underlying malignant tumour or a meningioma respectively. A calcified pineal gland may be displaced from the midline by a tumour mass. Raised intracranial pressure may give rise to erosion of the clinoid processes which may also result from tumours arising near the pituitary. The pituitary fossa may be expanded by an adenoma therein.

ELECTROENCEPHALOGRAPHY. Abnormally slow waves may localise a tumour in the cerebral hemispheres. Diffuse slowing may arise as a result of raised intracranial pressure from tumours situated above or below the tentorium.

ECHO-ENCEPHALOGRAPHY. Ultrasonic waves are reflected back from midline structures in the brain and displayed on a cathode ray tube. Displacement of these structures can be shown and hence space-occupying lesions can be lateralised. The procedure is simple and rapid in execution and can be carried out at the bedside.

RADIO-ISOTOPE ENCEPHALOGRAPHY. Isotope-encephalography, also known as 'brain scanning', depends for its effectiveness on a concentration, greater in cerebral tumours than in normal brain tissue, of an isotope (usually technetium) given intravenously. It is particularly successful in outlining meningiomata, less accurate in demonstrating gliomata and least effective in revealing metastatic tumours and those tumours situated in the posterior fossa.

CEREBROSPINAL FLUID. Lumbar puncture should rarely be carried out if there is evidence of raised intracranial pressure and never in such circumstances unless neurosurgical help is rapidly available. If there is clear evidence of a space-occupying lesion in the brain, examination of the CSF is usually unnecessary and unhelpful. Where a meningitic picture is present and no tumour mass can be demonstrated the diagnosis of carcinomatosis of the meninges may be made by examination of the CSF, whose sugar content is reduced and which may contain tumour cells.

ARTERIOGRAPHY. The intracranial vessels, outlined by a radio-opaque dye injected into the carotid or vertebral arteries, may be displaced in the region of a tumour, and the appearance of the vessels may indicate the pathological nature of the lesion. The procedure is relatively safe and does not upset the balance of intracranial pressure as does pneumoencephalography.

PNEUMOENCEPHALOGRAPHY. Air injected into the cerebrospinal fluid by lumbar puncture to replace an equal volume of fluid (20-30 ml) may be used as a contrast medium which can be manipulated to the various parts of the ventricular and subarachnoid space by suitable positioning of the head, thus enabling enlargements or displacements of the ventricular system and atrophic dilatations of the cortical sulci to be recognised. In the presence of raised intracranial pressure air is introduced directly into the ventricles through a burr hole in the skull (ventriculography). This diminishes the risk of impacting the brain stem in the foramen magnum but the danger of secondary rise in pressure from expansion of the air is sufficiently great to limit this investigation to a pre-operative procedure. A less risky procedure with special applications is to introduce a radio-opaque medium such as Myodil into the ventricles through a brain cannula.

Diagnosis. It is essential that cerebral tumour be diagnosed before signs of raised intracranial pressure appear. This can be done only if the possibility of a tumour being present is considered in every case presenting cerebral symptoms for the first time and if careful examination, continued observation and, if necessary, special investigations are carried out in suspected cases. The differential diagnosis depends largely on the presenting clinical features which may be headache (p. 838), epilepsy (p. 827) or manifestations of a focal lesion in a particular area. Other space-occupying lesions such as abscess or subdural haematoma must also be borne in mind.

Treatment. Medical treatment of tumours can never be anything more than temporary or palliative. Medical measures for relief of raised intracranial pressure are often demanded in circumstances when surgery is not available or when the patient's life is threatened before investigation has revealed the diagnosis. This can best be achieved by the administration of dexamethasone 4 mg four times daily, initially given by injection and later by mouth; striking improvement in a patient's conscious level is often produced and sometimes regression of focal disabilities. The use of intravenous hypertonic solutions has largely been supplanted by treatment with dexamethasone but the intravenous administration of 50 per cent sucrose or of a 15 per cent solution of mannitol or of a 30 per cent solution of urea can produce marked but short lived reduction of intracranial pressure.

Cytotoxic drugs, such as cyclophosphamide have been administered either systemically or through a carotid artery for treatment of malignant cerebral tumours. This treatment is still in an experimental stage and at present seems to offer little more than temporary palliation.

The definitive treatment of intracranial tumours is surgical. When possible the whole of a tumour should be excised but complete removal of the tumour depends on a number of factors. The tumour may be inaccessible and thus its exposure may be attended by unacceptable brain damage. It may invade areas where excision of small amounts of tissue may cause major disability as is particularly likely to happen in the brain stem or in areas of the dominant hemisphere.

In general benign tumours such as meningiomas and neuromas offer the best prospects for complete removal without unacceptable damage to vital structures. Meningiomas can usually be totally excised and rarely is there any recurrence. Meningiomas of the olfactory groove, those in the suprasellar area and those over the convexity of the hemispheres have a particularly favourable prognosis. Often, meningiomas of the inner part of the sphenoidal ridge and within the cerebello-pontine angles cannot be completely removed but their partial excision results in long continued improvement. Even after a successful removal of a meningioma, a number of patients may develop recurrent fits.

Craniopharyngiomas, though benign, can sometimes be completely removed but often the closeness of the hypothalamus prevents total excision. Pituitary adenomas can usually be extirpated and even when only incomplete excision is possible further visual loss is prevented.

Colloid cysts of the third ventricle and other intraventricular neoplasms can often be removed but sometimes their complete excision is technically very difficult.

Malignant gliomas cannot be removed completely though favourably situated tumours may benefit markedly for a time from partial removal.

Less malignant slow growing tumours such as Grade 2 astrocytomas and oligodendrogliomas, though they can rarely be completely excised may benefit for many years from partial removal. The prognosis for cystic astrocytoma is particularly good if the cyst is drained and as much as possible of the tumour removed. Medulloblastoma of the cerebellar vermis, found in childhood, cannot be completely excised and surgery produces little improvement.

There is a place for palliative surgery even when complete excision of a tumour cannot be attempted. Partial removal or drainage of a cyst is often of benefit. Decompression and hence relief of raised intracranial pressure may be produced by removing part of the tumour or excising normal brain tissue in the frontal or temporal lobes. Removal of part of the skull vault is also effective in reducing pressure. Internal hydrocephalus may be relieved by a short circuiting procedure in which a drain is placed in one of the lateral ventricles and led into the cisterna magna.

The precise surgical approach and the prognosis for a cerebral tumour can be assessed only in the light of its site, its pathological nature, its blood supply and the degree of disability it causes. Early treatment is particularly important for those tumours which are susceptible to complete removal and which menace life or sight. Early diagnosis of acoustic neuromas and pituitary tumours markedly improves the outlook for their treatment.

Prognosis. Death is inevitable if a cerebral tumour cannot be removed though it may be postponed by palliative decompression; even so, the average expectation of life is less than six months in the case of the more malignant growths. Benign tumours can be removed completely if they grow in an accessible part of the brain as can gliomas, or even a solitary metastatic tumour, when they are in a part of the brain such as the frontal lobe or cerebellum which can be sacrificed with relative impunity.

HEADACHE

Headache is perhaps the most common symptom a doctor is asked to treat. There is a particular anxiety related to this pain because of its association with the brain, 'the organ of the mind'. The brain itself is insensitive but some intracranial structures have receptors for pain. These are the major venous sinuses, the arteries round the base of the brain and the meningeal arteries and the dura of anterior and posterior fossae (but not the middle fossa). All the extracranial tissues are pain sensitive. The most important mechanisms underlying headache are vasodilatation, traction on intracranial structures, inflammation, muscle spasm, referred pain and psychogenic headache.

Clinical Features. *Vascular Headaches.* Dilatation of intracranial vessels is responsible for the headache in influenza and other systemic infections, the headache which follows an epileptic fit (p. 828), post-traumatic headache, and the headache associated with high altitudes, hypercapnia and the use of vasodilator drugs such as histamine, nitrites and alcohol. Abrupt elevation of blood pressure may cause headache in this way. Vascular headache is typically throbbing in type. The headache of migraine and chronic hypertension on the other hand is due to dilatation of extracranial arteries.

Traction on Intracranial Structures. In addition to distension, traction on the great vessels and dura at the base of the brain causes headache. Pain is momentarily increased by sudden movement of the head. Occasionally pain of this nature indicates the localisation of a cerebral tumour (p. 833). The value of headache as a localising sign is reduced by the fact that pain may be referred to another part of the head but if unilateral it does help to indicate the side of the tumour.

Inflammation. Meningeal irritation, whether due to meningitis, haemorrhage or other cause produces generalised headache which is accentuated by head movement, coughing or straining. Involvement of the roots of the cranial nerves contributes to headache by causing spasm of occipital and nuchal muscles. Neck stiffness is an important sign of meningeal inflammation (p. 856). Extracranial inflammation usually causes more localised headache. Cranial arteritis (p. 306) is a disease of later life characterised by localised throbbing pain in the head, sometimes associated with arteritis in other parts of the body. Tenderness is localised over and around an inflamed temporal artery and if a segment of a vessel is removed for biopsy the pain often disappears.

Muscle Spasm. This is one of the most common mechanisms of headache. Contraction is commonly due to emotional tension, producing the most persistent type of headache which varies in intensity from a feeling of tightness to a true aching pain. It may be unilateral but is usually bilateral. Nodular areas and points of tenderness may be palpated in the painful muscles or along the occipital and supraorbital ridges. Secondary muscle spasm may contribute to a prolonged pain referred from other structures. It may also be caused by irritation of cervical nerve roots by cervical spondylosis (p. 890) though this is probably overestimated as a cause of headache.

Referred Headache. Disease of structures in the head may cause pain referred to the cranium. Eye disease such as glaucoma and iritis causes frontal headache. Ciliary spasm induced by some errors of refraction may cause pain but 'eye strain' is certainly not a common cause of headache. Nasal and sinus disease causes pain in the malar, nasal and frontal areas which responds to nasal vasoconstrictors. Dental, aural and temporo-mandibular joint diseases may cause pain spreading far beyond the area of primary pain.

Psychogenic Headache. By far the most common cause of headache is emotional upset. It is often vascular or tension in type but may assume peculiar qualities which have features suggesting a mechanism of conversion hysteria (p. 923). It is often a sense of pressure at the vertex or a tight band round the head, constant day and night, and completely resistant to analgesic drugs though it may respond to non-analgesic sedatives. There is usually an underlying personality defect in this type of 'functional headache' which is much rarer than the vascular or tension types.

Treatment. Headache may disappear after removal of a primary cause such as systemic infection, ocular or sinus disease, or of a simple psychological problem. Otherwise the treatment is symptomatic. Aspirin (300-600 mg) and other simple analgesics are valuable but opiates should be avoided. Psychogenic headache is resistant to all treatment except psychotherapy. If the mechanism is vascular it may be advisable to use the treatment recommended for migraine (p. 841) and muscle tension headache may respond to tranquillisers such as chlordiazepoxide or diazepam.

Migraine

Migraine is characterised by periodic headaches which are usually unilateral and are often associated with visual disturbance and vomiting.

Aetiology. The condition is believed to be due to a disturbance in the carotid or vertebro-basilar vascular tree. An initial phase of vaso-constriction causes symptoms of local cortical or brain stem ischaemia and this is followed by vasodilatation. These changes affect both intra- and extracranial arteries and it is dilatation of the extracranial vessels which causes pain by stretching the pain nerve-endings in the arterial wall. Pain may be prolonged by secondary muscular contraction.

There is a genetic predisposition; approximately three-quarters of patients who suffer from migraine have close relatives similarly affected.

Migrainous attacks may be precipitated by a variety of factors such as menstruation, flashing lights, stress and anxiety. Cheese, chocolate, sherry and red wine are common precipitants and are all rich in tyramine; experimental ingestion of tyramine will often promote an attack. Reserpine, which liberates 5-hydroxytriptamine (serotonin) in brain, can also cause migraine. It is of interest that some serotonin antagonists are helpful in treatment. The significance of these findings is not yet clear but it seems likely that, in some and perhaps many instances, migraine is mediated by one or more biochemical disturbances.

Clinical Features. The condition usually starts after puberty and continues until late middle life. Headache occurs in paroxysms which are often related to emotional stress, particularly during the period of relaxation when the stress is over. Attacks occur at intervals which vary from a few days to several months. The first symptom of an attack is due to vasospasm. This is commonly a sensation of white or coloured lights, scintillating spots, wavy lines, or defects in the visual fields. Paraesthesiae or weakness of one half of the body may be experienced or there may be numbness of both hands and around the mouth. These symptoms may last up to half an hour, and are followed by headache which usually begins in one spot and subsequently involves the whole of one side of the head; this may be the same or the side opposite to the visual or sensory symptoms. The side affected is not constant with each attack and the headache often becomes bilateral. The pain is usually severe and throbbing in character and is associated with vomiting, photophobia, pallor, sweating and prostration which may cause severe loss of muscle tone and necessitate the patient taking to her bed in a darkened room. The attack may last from a few hours to several days and it leaves the patient weak and exhausted. In rare cases the cerebral changes may last for several days, particularly if the motor area is involved (hemiplegic migraine). Permanent cortical damage may result, usually leaving a visual scotoma of cortical type (p. 813).

Diagnosis. This is based on the periodic nature of the disturbance, the family history and the absence of abnormal physical signs. Rare cases of headache resembling migraine are caused by a cerebral aneurysm or angioma ('symptonatic migraine'). In these cases the pain is unilateral and usually associated with ocal signs.

Treatment. Any anxiety about the cause of the headaches must be relieved. While it is rarely possible to alter significantly the stresses of a patient's life, it is practicable to avoid such precipitants as flashing lights and various dietary factors. Regular medication is essential for those whose lives are being disrupted by migraine and this consists of a prophylactic drug together with a remedy which aborts attacks of migraine when they occur. Mild tranquillisers such as diazepam 2 mg twice daily are particularly helpful in reducing the frequency of attacks. When simple measures are ineffective, methysergide (1-2 mg thrice daily), a serotonin antagonist, may suppress migraine. Unfortunately it produces side-effects, particularly muscle cramps and insomnia. More serious reactions include peripheral vasoconstriction and, rarely, retroperitoneal fibrosis. Methysergide should not be given to patients with vascular disease, to elderly persons or to pregnant women. Otherwise it should be used only in those patients who have not responded to simpler measures and whose attacks are very frequent, severe and disabling.

Treatment of an acute attack is based on the use of ergotamine given as early as possible during the development of the episode. It is not effective when headache has become established. Tablets of 1 mg of ergotamine tartrate held under the tongue are rapidly absorbed and often abort an attack at its inception. Even more rapid absorption is obtained when ergotamine is administered in aerosol form using an inhaler containing a fine powder packed under pressure. The powder should be inhaled deeply when the inhaler is activated; in this way 0·3 mg of ergotamine can be administered and is rapidly absorbed. This regime may be repeated three or four times at five-minute intervals at the beginning of an attack. Unfortunately all the oral methods of administration frequently produce intolerable nausea and vomiting. In such circumstances ergotamine suppositories are available and are sometimes helpful. If the patient is capable of giving his own injections, ergotamine tartrate (0·5 mg) by the subcutaneous or intramuscular route, can be an effective method of stopping an attack.

Other drugs have been used. Monoamine oxidase inhibitors, tricyclic antidepressant drugs or clonidine occasionally help. The administration of chorionic gonadotrophin is said to reduce the number of attacks of migraine in some women. In those whose migraine tends to occur a few days prior to the menstrual periods, a diuretic is sometimes of prophylactic benefit. It is difficult to evaluate different methods of treatment because of the variable nature of migraine and because of the marked tendency of sufferers temporarily to respond to placebo treatment. Even so at least 80 per cent of patients can be markedly improved by rational therapy.

DISORDERS OF THE BLOOD VESSELS

The blood supply required by the brain does not vary significantly when the brain is active. As it has no means of storing energy or functioning by anaerobic metabolism the brain is particularly vulnerable to disorders of its circulation and so lesions of the cerebral blood vessels are among the most common causes of neurological disease. The brain tissue may be damaged by haemorrhage or rendered ischaemic by an inadequate blood supply. Three factors have to be considered in cerebrovascular disease:

1. *Vascular Disease*. Pathological change must be present in one or more of the arteries supplying the brain. This may be a local abnormality such as aneurysm or arteriovenous malformation or part of more widespread arterial disease. The most common vascular disorders are atherosclerosis and hypertension. Inflammatory disorders such as syphilitic endarteritis, thrombo-angiitis obliterans and polyarteritis are rare causes of cerebrovascular disturbance but recognition is important as specific treatment may be possible. Any of these may be the underlying cause of haemorrhage or thrombosis. The final accident depends on one or other of the following factors.

2. *Circulatory Dynamics*. Haemorrhage occurs if pressure rises rapidly within a pathological vessel and an existing hypertension makes it more likely that a further rise will exceed the capacity of the damaged vessel to accommodate it. Conversely if pressure falls excessively the flow through a stenosed vessel may be insufficient to enable proper functioning of the brain in its distribution area. Temporary ischaemia causes temporary neurological disturbance but if ischaemia lasts for more than a few minutes infarction of the brain occurs. Hypotension also predisposes to thrombosis within a damaged blood vessel and infarction is then almost inevitable. Infarction may also result if a major vessel is suddenly occluded by impaction of an embolus without any underlying vascular disease in the brain.

3. *Clotting Disorders*. Primary thrombotic diseases very rarely cause cerebral arterial thrombosis. Spontaneous thrombosis may, however, occur in the cerebral veins or dural sinuses (p. 851). Bleeding disorders (p. 758) may cause cerebral purpura and areas of softening may coalesce and lead to more severe haemorrhage as is not uncommon in acute leukaemia of children. Cerebral haemorrhage may be the cause of death in idiopathic thrombocytopenic purpura.

Cerebral Atherosclerosis

This is a disease of late middle life and old age affecting the sexes equally.

Pathology. The progressive obliteration of many cerebral arteries leads to ischaemia which causes degeneration of cells and fibres giving rise to multiple small areas of atrophy, particularly of the grey matter. There is normally an excellent collateral circulation in the brain and this minimises the damage caused by even advanced stenosis, but the compensation becomes inadequate (circulatory insufficiency) if the systemic blood pressure drops appreciably or if narrowing of a collateral vessel occurs. Occlusion of a vessel is followed by necrosis of the cerebral tissue which is replaced by a glial scar, or a cyst may form.

Clinical Features. The onset is usually insidious but may be marked by a minor cerebral infarction. The clinical picture will depend on the area of the brain which is mainly involved but it is commonly a progressive impairment of the higher faculties such as loss of intellectual capacity, impairment of memory for recent events, defective judgement and emotional lability. Selfishness, resistance to change, querulousness and the appearance of paranoid ideas are common features. Impairment of self-control may involve the patient with the authorities because of some public offence.

Physical symptoms may occur with the mental disorder or as the sole abnormality. If caused by brief circulatory insufficiency they may be transient, but recurrent small infarcts lead to a cumulation of minor or major neurological defects which depend on the regions affected. There may be dysphasia, hemiplegia or brain stem symptoms and the signs may be bilateral. A double hemiplegia may leave as a residue a form of pseudobulbar palsy with spasticity of the tongue, dysarthria, emotional lability and bilateral signs of an upper motor neurone lesion. Epilepsy may occur and a Parkinsonian picture develops when the brunt of the ischaemia falls on the basal ganglia (p. 875). These lesions may cause their appropriate physical signs but otherwise it is difficult to differentiate the condition from other causes of pre-senile or senile dementia (p. 941). The CSF usually shows no abnormalities though occasionally there is a slight rise in the protein content. There are no specific radiological or EEG abnormalities ~~though the~~ latter will show diffuse signs of local brain damage.

Diagnosis. The main problems are to distinguish cerebral atherosclerosis from other causes of dementia and from cerebral tumour. The pre-senile dementias of Pick and Alzheimer occur earlier and physical signs are much less evident. Neurosyphilis usually occurs earlier and gives rise to Argyll Robertson pupils and a positive Wassermann reaction. The diagnosis of chronic alcoholism and chronic subdural haematoma may be an exceedingly difficult problem if these diseases are not borne in mind when taking the history. Cerebral tumour may cause a similar mental state but physical signs are likely to be unilateral. Nevertheless if this possibility cannot be excluded it may be necessary to investigate further with isotope encephalography and other tests (p. 836).

Treatment. There is no specific treatment but much can be done to avoid difficulties. Vasodilator drugs are of no value. Epileptic attacks should be controlled by anticonvulsant therapy, and every effort should be made to keep the patient as active as possible. He should not be allowed to undertake matters requiring unimpaired judgement and is best advised to retire from business worries. Confusional states may occur if the patient is moved to an unfamiliar place such as a hospital but this may be required in the later stages.

Prognosis. Degenerative vascular disease is a progressive disorder, the duration of which depends on how soon a major vascular occlusion occurs. This may be postponed by protecting the elderly patient from factors which are likely to cause hypotension. The importance of restoring the blood pressure in elderly people with haematemesis, myocardial infarction, etc., is emphasised. Anaesthetics often make these patients much worse; hypotensive drugs must be used with caution, and the unnecessary use of hypnotics is to be deprecated.

Imp!

Cerebral Arterial Thrombosis

This may occur at any age according to the cause, in children as a complication of acute fever, in young adults due to meningo-vascular syphilis and in old people due to atherosclerosis.

Clinical Features. In common with other vascular disorders, arterial thrombosis causes maximum disability within a short time but there is later some recovery. Nevertheless, in comparison with haemorrhage and still more with embolism, the onset of symptoms in thrombosis is comparatively gradual, symptoms continuing to develop over several hours or even one or two days. This mode of onset causes less generalised disturbance of cerebral function. The patient is often dazed and may have an epileptic seizure at the onset, but consciousness is usually retained. The focal signs depend on the area of brain that is involved (p. 808). Hemiplegia, due to infarction in the territory of the middle cerebral artery, is the most common disability and there may also be hemianaesthesia and hemianopia. The obstruction to blood flow may be in the middle cerebral artery or one of its branches, but a similar picture will result from stenosis or occlusion of the internal carotid artery just beyond its origin from the common carotid artery in the neck, or of the main vessels as they arise from the arch of the aorta. The most common of these sites is the internal carotid artery. This is the probable site if there are recurrent transient episodes of weakness or sensory symptoms on the opposite side ('stuttering hemiplegia') and the localisation is certain if there is a history of one or more brief attacks of blindness or flashing lights in the visual field of the eye on the side of the lesion. This is due to ischaemia of the retina of that eye as the ophthalmic artery which supplies it branches from the internal carotid artery just below its intracranial bifurcation. Visual symptoms are transient because circulation is restored by collateral vessels from the orbit, and the rich intracranial anastomosis accounts for the temporary nature of many of the cerebral symptoms; indeed complete occlusion of the internal carotid artery may occur without causing symptoms. Palpation of the internal carotid artery in the neck may reveal diminished pulsation but a more valuable sign is a bruit. The pressure required to occlude circulation in the retinal arteries may be measured with an ophthalmo-dynamometer. It may be reduced on the side of carotid occlusion during the acute stage until circulatory adjustment takes place.

Similar lesions occur in the vertebro-basilar territory, transient or permanent signs of damage to brain-stem structures and the occipital area of the cerebral cortex being found. The more common symptoms are vertigo, deafness, diplopia, sudden loss of muscle tone causing the patient to fall, loss of consciousness, ataxia and cortical blindness. An attack may resemble migraine. Infarction is commonly limited to the area supplied by a single branch of the basilar or a vertebral artery. One of the most readily diagnosed is infarction of the postero-lateral part of the upper medulla and of the adjacent part of the cerebellum due to occlusion of the posterior inferior cerebellar artery or the vertebral artery from which it arises. The latter may be distorted by osteophytes of cervical spondylosis as it passes upwards through the transverse processes of the cervical vertebrae.

Treatment. Infarction due to stenosis or thrombosis of intracranial arteries does not benefit from anticoagulant therapy but recurrent transient ischaemic episodes may be treated with anticoagulants on a long-term basis in the hope of preventing a major stroke. If stenosis of the internal carotid or vertebral artery is suspected, it should be confirmed by arteriography and then relieved by surgery, or the patient placed on long-term anticoagulant therapy. The management of the stroke is described on page 847.

Prognosis. The outlook depends on the site and extent of arterial involvement. If the patient survives the acute stage some recovery of function may be expected during the first one to two months but residual damage is almost certain if infarction has occurred. One thrombosis is often followed sooner or later by another.

Cerebral Embolism

Unlike other causes of circulatory disturbance, embolism may damage a brain which has previously had healthy blood vessels. An embolus most often lodges in the left middle cerebral artery and arises from sources of thrombus in the arterial side of the circulation. Common causes are atrial fibrillation (especially when it is intermittent or terminated with quinidine), mural thrombus after myocardial infarction, infective endocarditis and clot or fragments of heart valve dislodged during cardiac surgery. Thrombosis in peripheral veins rarely causes cerebral embolism except when the embolus can reach the arterial circulation by passing through a septal defect (p. 293) (paradoxical embolus). Air or fat may enter the arterial circulation after injury to the thoracic cage, long bones or perinephric tissue and the resulting cerebral infarction is similar to that caused by blood clot.

Clinical Features. Of all vascular catastrophes embolism is the most abrupt in onset. This feature should always suggest embolism though the diagnosis can only be tentative unless a source for the embolus can be demonstrated. Loss of consciousness or a seizure may be present but often the patient is only dazed and confused. The signs depend on the site of infarction. The condition may progress due to spread of thrombosis proximal to the embolus, or may regress due to the embolus passing more peripherally. Secondary haemorrhage is common so that red cells may be found in the cerebrospinal fluid, complicating the diagnosis. Frequently the fluid is normal.

Treatment. The treatment during and after the stroke is described on page 847. Anticoagulant therapy should be started immediately because of the danger of further emboli. It is not certain how long this should be continued but there is probably only a small risk if treatment is withdrawn after six months. It may also be possible to remove the primary source of emboli.

Prognosis. Embolism is rarely fatal and the prognosis will depend largely on the source of the embolus. The neurological deficit improves to some extent as oedema and neuronal shock subside, but there may be residual symptoms according to the extent of the cerebral damage.

Intracerebral Haemorrhage

This is a common cause of a stroke or apoplexy in people who have both hypertension and atherosclerosis.

Pathology. Bleeding may occur with any disease of the intracranial vessels but most commonly with atherosclerosis and aneurysm. Rupture is usually precipitated by abrupt rise of blood pressure occasioned by physical or emotional stress but sometimes is apparently spontaneous. Coagulation defects are rare causes. The effused blood destroys cerebral tissue and later forms a haematoma or a cyst. More often early death occurs as the blood bursts through to the ventricles or to the surface of the brain where it enters the subarachnoid space. Spontaneous intracerebral haemorrhage most often occurs from the lenticulostriate branch of the middle cerebral artery in the external capsule and rapidly involves the internal capsule. The pons is also a frequent site (where bleeding is usually fatal) but haemorrhage may occur from any intracerebral artery.

Clinical Features. The onset is rapid with focal signs according to the site of haemorrhage. About half of the cases lose consciousness within a few minutes. Before consciousness is lost, headache may be complained of and vomiting is common at the onset. Neck stiffness may be found. The rapid displacement of the brain stem causes coma with loss of muscle tone, stertorous breathing and slowing of the pulse and respiration. The face is often congested. Pupils may be unequal. If the haemorrhage is pontine the pupils become pinpoint in size and temperature rises to 40° C. or higher. The more common external capsular haemorrhage causes contralateral hemiplegia. At first the head and eyes are deviated to the side of the lesion and the loss of tone is greater in the muscles of the contralateral side of the body. The plantar reflex is extensor on the limp side. The naso-labial fold on that side is flattened and the cheek blows in and out on respiration. If the patient survives, the depth of coma lessens in a few days, restless movements appear, and tone returns to the paretic side. The head and eyes now tend to deviate towards the paralysed side and signs of spasticity appear on that side. On recovering consciousness the patient may be dysphasic if the haemorrhage has affected the dominant hemisphere and contralateral sensory or hemianopic defects may be found. Voluntary movement gradually returns to the proximal muscles of the hemiplegic limbs, but the skilled movements of the hand may be permanently lost. The amount of recovery depends mainly on the extent of the damage. The initial recovery is fairly rapid but the tempo slows down after the second month. The initial improvement is attributed to recovery from 'neuronal shock'. This concept, due to Hughlings Jackson, is applicable to all acute vascular and traumatic lesions of the central nervous system. It is considered that sudden lesions may temporarily suppress the function of neurones which are, however, capable of resuming function at a later date. Neurones damaged beyond the stage of recovery are not capable of regeneration. Some functional recovery is, however, possible by taking advantage of the capacity of the central nervous system to perform functions in different ways. The first order sensory neurones and the lower motor neurones are uniquely necessary and their loss cannot be replaced.

Diagnosis

Cerebral Haemorrhage, *Thrombosis*, *Embolism*. These lesions can sometimes be distinguished from each other. A sudden onset and a source of emboli point to an embolism; the rapid development of a stroke, often with loss of consciousness, in a hypertensive patient suggests a haemorrhagic lesion; a more gradual onset indicates a thrombotic process. However, the differentiation of these vascular lesions can rarely be achieved with certainty on clinical grounds alone and even after full investigation small intracerebral haemorrhages may be confused with infarcts due to occlusive lesions.

Subarachnoid Haemorrhage. The onset is sudden, signs of meningeal irritation are present and the CSF contains blood.

Cerebral Tumour. Tumours, particularly metastases, may sometimes present with rapidly developing signs and mimic a vascular lesion. Five per cent of 'strokes' are due to cerebral tumour. Headache may indicate the true diagnosis but often this is revealed only by the subsequent progression or by investigation.

Treatment. There is no certain method of arresting intracerebral haemorrhage. If the blood pressure remains persistently high it should be lowered gradually by antihypertensive drugs (p. 279), a careful watch being kept for fresh neurological signs. When consciousness has returned arteriography should be carried out if the history suggests that the cause of the bleeding is a local vascular lesion such as an aneurysm. This may also be desirable if the history, physical findings and EEG record suggest that there is a localised haematoma in a region of the brain which can be explored surgically as it may be possible to aspirate the clot and coagulate the bleeding point. This procedure should be especially considered in the patient who shows signs of a progressive focal lesion after recovering consciousness.

Apart from measures directed at preventing further vascular damage, the *management of the patient who has had a stroke* is essentially the same irrespective of the cause. The immediate problem is the nursing of an unconscious patient which involves the maintenance of a clear airway, avoidance of respiratory infection, care of the skin, bladder and bowel, and the provision of fluids and food by an intragastric tube. Passive movements of all limbs should be begun from the outset to prevent the development of contractures, and active movements started as soon as the patient has recovered sufficiently to co-operate. These should be performed against gradually increasing resistance. When power is returning, skilled movements should be re-established by carefully chosen occupational therapy. Early mobilisation and vigorous rehabilitation are essential. The patient should be propped up within 48 hours of recovering consciousness, encouraged to use the limbs and got out of bed as soon as he is able to support himself in a chair. Recovery of postural reflexes is facilitated in this way. Walking should soon be re-established, the optimum method being taught by a physiotherapist. It may be necessary to use aids such as a toe-spring or below-knee caliper. Unfortunately the return of upper limb function after hemiplegia is usually less satisfactory, but the difference between a useful and a useless limb may be determined by the physical treatment given during the first weeks of the illness.

Prognosis. Cerebral haemorrhage is commonly fatal and recovery is unlikely if coma lasts longer than 48 hours. If the patient survives, some functional recovery is probable but it will not be complete. In hemiplegia, the lower limb often recovers sufficiently for the patient to be able to walk, especially with the aid of such devices as a caliper or a toe-spring. Functional recovery of the upper limb is seldom adequate for useful function and dysphasia due to haemorrhage rarely improves.

Hypertensive Encephalopathy

This is a transient disturbance of cerebral function associated with high blood pressure and is discussed on page 276.

Cerebral Aneurysms

Aetiology and Pathology. Congenital aneurysms are more common within the skull, especially in the vessels comprising the circle of Willis and particularly in its anterior part. Aneurysms, which are frequently multiple, occur at the bifurcation of an artery where there is a congenital defect of the medial coat and often a small anomaly of branching. The medial defect permits local distension of the vessel wall when the blood pressure rises in later life. For this reason clinical manifestations usually occur after the age of 40. They are equally common in both sexes.

Clinical Features. Many cerebral aneurysms cause no symptoms and are found at routine post-mortem. Symptoms may occur in three ways: (*a*) focal pressure symptoms, (*b*) spontaneous subarachnoid haemorrhage, (*c*) intracerebral haemorrhage or infarction. There may be local or generalised headache. This occasionally simulates migraine especially if accompanied by transient focal cerebral symptoms but is distinguished by the fact that it always occurs on the same side and does not vary in successive attacks like true migraine. The most common pressure effect is third nerve palsy (p. 815) as aneurysms may be in relation to this nerve at several sites in the circle of Willis and in the posterior fossa. Aneurysm of the internal carotid artery within the cavernous sinus presses on the optic nerve or chiasma, the third, fourth or sixth cranial nerves and the first and second divisions of the fifth nerve. Thus, there may be visual failure, ptosis, diplopia or pain and sensory loss on the face. Signs of raised intracranial pressure do not occur as the aneurysms are small in size.

There may be no evidence of intracranial aneurysm until the onset of subarachnoid haemorrhage. Before a major haemorrhage there is often a series of small leaks which cause headache or pain and stiffness in the neck and shoulder. Infraclinoid aneurysms in the cavernous sinus cannot, of course, bleed into the subarachnoid space. Rupture into the cavernous sinus causes unilateral pulsating exophthalmos as the arteriovenous fistula transmits arterial pulsation to the orbit. A loud bruit may be heard over the eye on the affected side. Otherwise a bruit is rare in cerebral aneurysms. Aneurysm rupturing into the brain causes intracerebral haemorrhage which is indistinguishable from that due to other causes and it may be the underlying lesion in transient cerebral ischaemic attacks or infarction by causing arterial spasm or thrombosis.

Diagnosis. Aneurysm presenting as a focal lesion must be distinguished from other causes of visual failure (optic neuritis, neoplasm), other causes of diplopia (disseminated sclerosis, syphilis) and of headache and subarachnoid haemorrhage. Leaking aneurysm may be mistaken for meningitis or 'rheumatism' of the neck and shoulders.

Treatment. The presence and site of the aneurysm must be confirmed by arteriography and surgical treatment undertaken (p. 850).

Prognosis. The aneurysm may remain stationary or may continue to expand, causing progressive focal signs, or may leak causing headache and mild meningeal irritation. Early recognition of the true nature of leaking aneurysm may enable the disaster of severe subarachnoid haemorrhage to be avoided as the danger of frank, and possibly fatal, rupture is ever present.

Subarachnoid Haemorrhage

Aetiology and Pathology. Bleeding into the subarachnoid space is commonly due to rupture of a congenital aneurysm but it may occur from an arteriovenous or capillary malformation, a ruptured atherosclerotic artery, head injury or rarely from a mycotic aneurysm in infective endocarditis. Bleeding from an infarct is rarely serious but subarachnoid haemorrhage may be the presenting symptom of the red infarct caused by cerebral venous thrombosis.

Clinical Features. There may be previous focal signs of pressure due to an aneurysm, especially diplopia (p. 815) or focal epilepsy from an arteriovenous anomaly. Symptoms of slight leaks from an aneurysm may precede frank rupture by weeks or months. Final rupture is sometimes precipitated by physical strain but is more often spontaneous. There is a sudden onset of severe headache, usually in the occipital region but passing into the neck and shoulders. In severe cases the patient feels as if he had been struck a blow but others may attribute the pain to a local cause in the neck. The patient may vomit at the onset and consciousness may be lost rapidly. Fresh focal signs may appear because of disruption of cerebral tissue by the haemorrhage or from vascular spasm in the vessel bearing the aneurysm and in other branches of the same parent vessel.

The findings on examination are:

Meningeal Irritation. Neck rigidity and Kernig's sign (p. 856) are usually present but may not be marked with slight haemorrhage. They are the most important clues to the nature of the stroke.

Focal Signs. These are present only if an aneurysm has caused local pressure effects or vascular spasm.

Signs of Raised Intracranial Pressure. (1) Coma tends to deepen rapidly and may be accompanied by (2) bilateral extensor plantar responses and the other manifestations of brain stem pressure such as (3) slowing of the pulse and (4) irregular or Cheyne-Stokes breathing (p. 245). (5) There may be a low grade pyrexia. (6) The sudden rise in pressure causes papilloedema in which swelling of the discs is slight but venous congestion and haemorrhage are marked. (7) Haemorrhage is retinal or subhyaloid.

The cerebrospinal fluid is under greatly increased pressure and is uniformly blood-stained. This can be confirmed by comparing the colour of three specimens collected successively from one lumbar puncture. The supernatant fluid of the centrifuged CSF should be xanthochromic if some hours have elapsed since haemorrhage. Blood cells may be seen in the fluid for about three days after a fresh haemorrhage, and xanthochromia may persist for three weeks. Slight proteinuria and glycosuria may be caused by the sudden brain stem compression. These findings should not lead to a conclusion that the stroke is associated with renal disease or diabetes mellitus.

Diagnosis

1. *Coma*. Other causes of loss of consciousness must be considered (p. 826). Only embolism compares with subarachnoid haemorrhage in rapidity of onset.
2. *Other Cerebrovascular Accidents*. A previous history compatible with leaking aneurysm is invaluable. Focal signs are more common and meningeal irritation less prominent in other cerebrovascular accidents. Blood may be found in the CSF in primary intracerebral haemorrhage and in bleeding secondary to infarction but is usually of lesser degree.
3. *Other Causes of Meningism* (p. 855). Meningitis has a slower onset and higher fever. The CSF contains leucocytes and organisms but no blood.

Treatment. The diagnosis is confirmed by lumbar puncture. The next stage of management is aimed at defining those cases in which the source of bleeding is a ruptured aneurysm which requires surgical treatment. Arteriography is an essential preliminary and should be performed as soon as possible if the patient is conscious and in good general condition. If the patient is comatose, angiography should be delayed until clinical improvement occurs. When no aneurysm can be demonstrated the principles of treatment are those applicable to strokes and set out on page 847.

If an aneurysm is present, surgical treatment may be aimed at clipping and occluding its neck or at proximal ligation of either the artery from which it arises or of the carotid artery in the neck. All of these methods are designed to prevent further haemorrhage. The danger of a second haemorrhage is greatest during the first 14 days, therefore unnecessary delay must be avoided. Premature surgical intervention may aggravate the condition of the patient by causing vasospasm, but when surgery is well timed it may reduce the mortality to less than 20 per cent. Recurrence of haemorrhage is improbable after two months and the risks of conservative treatment are then no higher than those of surgery. Conservative treatment is therefore appropriate for the mild case seen for the first time after the period of greatest danger from recurrence or for the case in whom the source of bleeding cannot be identified or in whom surgical intervention is too dangerous. These patients should be kept in bed for a period of about four weeks and then slowly rehabilitated. The choice of treatment requires careful joint consideration by physician and surgeon.

Prognosis. There is a great risk of death from subarachnoid haemorrhage due to ruptured cerebral aneurysm. In the absence of surgical treatment about 40 per cent of patients die in the initial attack. Of those who survive about one-third have a recurrence of bleeding which frequently develops while the patient is still in hospital for the first attack.

Cerebral Venous Thrombosis

Thrombosis of the intracranial venous sinuses is associated with (*a*) thrombophlebitis spreading from infection of the middle ear, accessory nasal sinuses, face and scalp; (*b*) thrombotic and dehydrated states such as polycythaemia, the puerperium, and in cachectic conditions in infancy and old age; (*c*) head injury without penetration of the skin. (*d*) There is evidence that oral contraceptives may cause cerebral venous thrombosis.

Lateral Sinus Thrombosis. This is usually associated with infection of the middle ear. There may be pain, oedema and venous congestion in the mastoid region from obstruction of the emissary veins which drain into the sinus. Thrombosis may extend to the superior longitudinal (sagittal) sinus without evidence of lateral sinus involvement.

Sagittal Sinus Thrombosis. This may be ushered in by fits, especially in children, as thrombosis spreads to cortical veins. As the cortex near the vertex is involved on both sides, signs of an upper motor neurone lesion involving the lower limbs (paraplegia) are commonly found. In other instances, especially in adults, thrombosis on the walls of the upper chamber of the sagittal sinus interferes with absorption of the cerebrospinal fluid causing hydrocephalus. The patient remains alert but complains of headache. Papilloedema may endanger eyesight.

Cavernous Sinus Thrombosis. This is the most serious type since it may give rise to septicaemia if it has been caused by infection. It may endanger the eye in the orbit which drains into the affected sinus. There is pain behind the eye and oedema of the eyelids. Exophthalmos and papilloedema may also be apparent and ocular palsies due to damage to the third, fourth or sixth nerve in the lateral wall of the sinus may be present.

Treatment. This is by antibiotics and anticoagulants. The majority of cases recover, but specialist advice should be sought as sight is endangered by prolonged papilloedema.

THE CEREBROSPINAL FLUID

The cerebrospinal fluid is secreted by the choroid plexuses in the lateral, third and fourth ventricles. It leaves the ventricular system through the apertures and flows through the cerebral and spinal subarachnoid spaces. It is returned into the venous sinuses by the arachnoid villi. In health, the fluid is clear and colourless. The pressure at the lumbar theca with the patient lying on his side is 50-150 mm of cerebrospinal fluid. It contains less than 5 lymphocytes per cmm and its important chemical constituents are protein 20-50 mg, glucose 50-80 mg, chloride (as sodium chloride) 700-750 mg all per 100 ml.

The patency of the cerebrospinal fluid pathway is tested by Queckenstedt's tests. One or both jugular veins are manually compressed while the CSF pressure is recorded in a manometer (estimations of pressure based on the rate of dripping from the needle are completely fallacious). If there is thrombosis of a jugular vein or obstruction in the cerebrospinal fluid pathway, as by a spinal tumour, the level of fluid in the manometer may not rise, or do so slowly and fail to fall when pressure is released. This result (positive) is found when the pathway for flow of fluid is reduced to a bore comparable with that of the needle; thus a negative result does not indicate that there is no compression of the spinal cord since a positive test does not occur until the block is almost complete.

Alterations in the characteristics of the cerebrospinal fluid are of great help in the diagnosis of neurological disease. The pressure may be raised in the presence of intracranial space-occupying lesions such as tumour and abscess, and also in acute inflammatory lesions such as meningitis. Bleeding into the cerebrospinal fluid (subarachnoid haemorrhage) is shown by blood in the fluid obtained by lumbar puncture (p. 850).

A rise in the cell count is encountered in infection of the nervous system, lymphocytes being the predominant cell in virus infections, neurosyphilis and tuberculous meningitis. Polymorphonuclear leucocytes predominate in pyogenic infections. Whether the infection is acute or chronic also influences the type of cell, as acute lesions are more commonly associated with an increase in polymorphonuclear leucocytes, whereas in chronic lesions a lymphocytosis is more usual. A marked increase in the cell count gives a turbid appearance to the CSF. A rise in the protein content of the CSF occurs in many conditions. An increase from the normal figure of 20-45 mg to several hundred milligrammes per 100 ml may be present in fluid below the level of a spinal tumour which is causing a block of the CSF pathway, and also in the presence of neurofibromata of the spinal or of the auditory nerves. The rise in protein associated with other cerebrospinal lesions is of much less degree, not usually exceeding 100 mg per 100 ml. The glucose content of the CSF is raised in diabetes mellitus. It is reduced in pyogenic meningitis and in tuberculous meningitis, in which diseases it is a valuable diagnostic and prognostic sign. The chloride content of the CSF is reduced in any condition associated with a low blood chloride level (p. 186). Routine estimations of sugar and chloride are unnecessary. Bacteriological examination of CSF is an important part of the investigation of a suspected infection of the nervous system.

The gamma globulin of the CSF is usually estimated and it normally comprises 5 to 15 per cent of the total protein. A rise in the proportion of gamma globulin above 30 per cent of the total protein is most often found in disseminated sclerosis, neurosyphilis and the connective tissue disorders. An indirect index of the gamma globulin in the CSF is given by the Lange curve which expresses the degree of precipitation of colloidal gold by increasing dilutions of CSF on a graduated scale from 0 to 5.

The Wassermann reaction and other serological tests for syphilis (p. 82) can also be determined in the CSF.

INFECTIONS OF THE BRAIN, SPINAL CORD AND MENINGES

Intracerebral Abscess

Aetiology. 1. Local spread by thrombophlebitis from an infected ear, paranasal sinus or from infection of the scalp or skull. This type is rare since the introduction of antibiotics.

2. Infected compound fracture of skull, either a penetrating wound of the convexity or a basal fracture involving a sinus.

3. Metastatic spread from bronchopulmonary infection or infective endocarditis.

Pathology. The initial infection spreads to surrounding brain causing suppurative encephalitis. The pus is slowly localised by a surrounding wall of gliosis which in a chronic abscess may form a tough capsule. Multiple abscesses, communicating or discrete, occur, particularly with metastatic spread.

Clinical Features. There are three main types of clinical history:

1. ACUTE ENCEPHALITIS. Soon after head injury or otitis media (in which aural discharge may be temporarily suppressed) the patient develops headache, vomiting and drowsiness passing to coma. Focal cerebral signs may be present and the temperature is raised.

2. SUBACUTE OR DELAYED ENCEPHALITIS. Head injury, cranial infection or infected embolism may be followed after weeks or months of apparent recovery by symptoms of encephalitis or of a chronic space-occupying lesion. During the latent interval there may be minor headache, irritability, malaise and intermittent pyrexia. These symptoms should lead to a search for a focal cerebral lesion in patients with infections such as otitis or bronchiectasis.

3. CHRONIC ABSCESS. This may follow one of the previous types of onset or there may be nothing to suggest that the lesion is infective. The chronic abscess

causes focal symptoms of a cerebral lesion (p. 808) and those of raised intracranial pressure which are indistinguishable from those of cerebral tumour. The temperature is usually normal or even subnormal. The most common sites for abscess secondary to otitis media are the cerebellum and the temporal lobe. Sinusitis and haematogenous spread may cause abscess in any part of the brain but most commonly in the frontal lobes.

Lumbar puncture may help to confirm the diagnosis but should be avoided if the diagnosis is highly likely and especially if localising signs suggest cerebellar abscess. The CSF pressure may be raised and there is usually an increase in cells up to 100 per cmm with a predominance of lymphocytes. The protein may be raised up to 200 mg per 100 ml; the chloride and glucose contents are normal and no organisms are found unless there is also a meningitis. The blood shows a polymorphonuclear leucocytosis and the ESR is often raised, but absence of these findings does not exclude chronic abscess.

Diagnosis. The presence of headache, personality change or unexplained ill-health in a patient with one of the causative diseases should suggest the possibility of cerebral abscess. Chronic abscess is often mistaken for cerebral tumour but this error will be minimised if careful otological and chest examinations are carried out in every case suspected of having an intracranial lesion. The EEG shows certain characteristic changes during the acute stage which may be valuable in diagnosis. As the diffuse encephalitis subsides changes in the EEG may be found which are very valuable for localisation of the abscess cavity or cavities. The radiological signs do not differ from those of cerebral tumour but radiological examination may show a causative lesion in ear, sinuses or chest.

Treatment. Prevention should be the first aim by efficient treatment of otitis media, sinusitis, fractures of the skull and bronchiectasis. Acute suppurative encephalitis is treated by immediate intramuscular injection of benzylpenicillin, 1-2 g followed by 600 mg four-hourly. Surgical assistance should be sought early and the abscess, localised by EEG and angiography, tapped with a brain cannula for aspiration of pus and instillation of antibiotics. Myodil, a radio-opaque iodine compound, is also instilled so that progress may be followed by serial radiography. Antibiotic medication is subsequently determined by the bacteriological findings. Measures to reduce intracranial pressure may also be required (p. 837). Excision of the abscess cavity may have to be undertaken at a later stage. In view of the high incidence of symptomatic epilepsy all patients should be given phenobarbitone prophylactically after the acute stage for a minimum period of two years.

Prognosis. About 15 per cent of patients with cerebral abscess die despite treatment and half of the survivors develop epilepsy. There may also be residual loss of neurological functions, depending on the site of the abscess. Rupture of the abscess into a ventricle or subarachnoid space causes meningitis which is usually fatal. The possibility of a recurrence of infection must always be borne in mind.

Spinal Epidural Abscess

This condition usually arises as a metastasis from infection elsewhere, often a boil, which may be so trivial as to be easily overlooked. Pain of root distribution is severe. It develops acutely and is followed by progressive loss of sensation and power in the lower limbs with sphincter disturbance. The signs are those of transverse myelitis (p. 887) but the local root irritation is the clue to the true cause. The temperature may be only slightly raised, but a polymorphonuclear leucocytosis is found in the blood. There may be radiological evidence of localised osteomyelitis of the spine. Paraplegia will become complete and irreversible if treatment is delayed. Large doses of antibiotics such as benzylpenicillin 600 mg four-hourly should be given immediately and the patient transferred to the care of a neurosurgeon without delay.

Meningitis

This is an inflammation of the pia and arachnoid membranes.

Aetiology and Pathology. Inflammation of the meninges may be sterile or infective.

Sterile. Blood in the CSF as in subarachnoid haemorrhage causes severe meningeal inflammation (p. 849). Meningeal irritation (‘*meningism*’) without inflammatory reaction occurs in acute specific fevers, otitis media and pneumonia in childhood. Cellular reaction (lymphocytic) may be associated with symptoms and signs of meningeal irritation in poliomyelitis (p. 867) and acute encephalomyelitis (p. 866). Carcinomatosis of the meninges is a rare cause.

Infective. Formerly the most common meningeal infections were due to meningococcal infection or infection with pyogenic organisms carried in the blood from a distant focus in the heart or lungs or introduced from without (e.g. a penetrating wound of the skull, an infected ear, a fracture involving an accessory nasal sinus or a lumbar puncture), or from within by rupture of a cerebral abscess. These types of meningitis have become rare since the introduction of the antibiotics has simplified treatment of the primary causes, and for similar reasons, tuberculous meningitis is now seldom seen in Britain. The most common infection is now viral. Rare infections are due to syphilis or to fungi.

The pia-arachnoid is congested and infiltrated with inflammatory cells. A thin layer of pus forms and this may later organise to form adhesions. These may cause obstruction to the free flow of CSF leading to hydrocephalus, or may damage the cranial nerves at the base of the brain. The CSF pressure rises rapidly, the protein content increases and there is a cellular reaction which varies in type and severity according to the nature of the inflammation and the causative organism. The sugar content of the CSF is decreased in bacterial infections and in carcinomatosis of the meninges. If the patient is not kept in electrolyte balance the chloride content may be reduced due to the loss of chloride by sweating and vomiting.

Meningococcal Meningitis

(Cerebrospinal Fever)

The meningococcus, spread by droplet infection, enters the body through the nasopharynx and is carried in the blood stream to the choroid plexuses and meninges where it enters the cerebrospinal fluid. This type of meningitis occurs sporadically especially in children, and in epidemics in children and young adults living in crowded conditions such as schools and barracks. Spread of infection may be due to symptomless carriers of the organism.

Clinical Features. The onset is acute, with headache, pyrexia and often rigors. The headache rapidly becomes severe and spreads down the neck. There may be pain in the back and in the limbs. Convulsions are common at the onset in children. Photophobia is usually present; the patient is irritable, resenting interference and lying curled up on his side. He becomes confused and drowsy and later comatose.

SIGNS OF MENINGEAL IRRITATION. These are prominent and present from an early stage:

Neck Rigidity. The patient complains of neck stiffness and the examiner is unable to put the patient's chin on his chest by passive flexion of the neck. When he attempts to do so the muscle spasm evoked makes the neck so rigid that the head and trunk may be lifted from the bed. Spasm may be so severe, particularly in children, as to cause head retraction.

Kernig's Sign. If the patient's thigh is flexed to 90° from the abdomen, it is then impossible to straighten the knee passively owing to spasm of the hamstring muscles. This manoeuvre stretches the roots of the sciatic nerve which are inflamed at their exits from the spinal theca.

SIGNS OF SEPTICAEMIA. There is often a petechial rash before the third day of the illness. Infection of one or more joints may occur; conjunctivitis is common, and adrenal failure, due to haemorrhage into the adrenal cortex (p. 660), is an occasional serious complication. Fulminating cases occur which deteriorate rapidly in contrast to chronic meningococcal septicaemia occasionally found in the elderly.

CEREBROSPINAL FLUID. This is under increased pressure but papilloedema is uncommon. The fluid is turbid and contains a thousand or more cells per cmm. These are almost entirely polymorphonuclear leucocytes; with Gram's stain these cells may be seen to contain Gram-negative diplococci. Failing this the meningococcus can be isolated by culture from the CSF and in the first few days from the blood. The protein content of the CSF is greatly raised and the glucose content markedly lowered. The blood shows a polymorphonuclear leucocytosis.

Diagnosis. The disease must be distinguished from the other causes of meningitis and meningism (p. 855). The onset of subarachnoid haemorrhage is more acute, the temperature much lower and the CSF is blood-stained. In neningism associated with pneumonia or acute infectious disease of children, he CSF pressure is increased but the fluid is clear and without cellular reaction.

Treatment. Treatment must be started without waiting for bacteriological onfirmation. If the fluid contains excess cells the patient should immediately e given sulphadiazine or sulphadimidine. The initial dose is 6 g for an adult nd 2 g for an infant, followed by 1 g four-hourly (or less in proportion to age) ntil the temperature is normal whereupon half the dose is given for a further ix days. This may be administered by mouth, but if the patient is unable to wallow or is vomiting, the intravenous or intramuscular route must be used. Sulphonamides must never be given intrathecally. The CSF should be examined twice in the first 24 hours after starting treatment. If there is no response to sulphadiazine after that interval penicillin may be given parenterally and intrathecally. General measures for the treatment of fever (p. 56) must also be carried out, special attention being paid to the maintenance of hydration and to renal function. Analgesics for the relief of pain and headache may also be required. For the treatment of acute adrenal failure see page 666.

Acute Pyogenic Meningitis

Infection by staphylococci, streptococci, pneumococci or *Haemophilus influenzae* sometimes occurs primarily in the meninges but it is more commonly secondary to infection in the heart, lungs, bones or elsewhere.

Clinical Features. Signs of meningitis are present and associated with signs of a local septic focus but there is no rash and other pyaemic signs are rarer than in meningococcal infection. Bacteriological examination of the cerebrospinal fluid establishes the diagnosis and should be performed without delay.

Treatment. Both sulphonamides and penicillin should be started immediately without waiting for bacteriological confirmation as the treatment can later be modified appropriately. Sulphadiazine 6 g by mouth is given at once followed by 2 g four-hourly. Benzylpenicillin 6 mg (10,000 units) mixed with 10 ml of the patient's CSF is injected intrathecally at the start of treatment but thereafter intramuscular injection is usually sufficient if given in large doses (at least 300 mg every four hours). For an infection with *H. influenzae*, the drugs of choice are chloramphenicol and ampicillin. For an adult 1 to 2 capsules each containing 250 mg of either drug should be given at six-hourly intervals. In all types of acute pyogenic meningitis treatment must be continued until the CSF has returned to normal and the temperature has been normal for at least two days.

Tuberculous Meningitis

Aetiology. The usual source of infection is a caseous focus in the meninges or brain substance adjacent to the cerebrospinal fluid pathway. The focus arises as a result of spread by the blood stream from a site elsewhere in the body.

The condition occurs most commonly shortly after a primary infection i childhood, but people of any age may be affected. The breakdown of the caseou focus may be due to head injury or to any illness causing diminished resistanc Tuberculous meningitis may occur as part of miliary tuberculosis.

Pathology. The brain is covered by a greenish, gelatinous exudate especiall around the base, and numerous scattered tubercles are found on the meninges

Clinical Features. In children the onset of tuberculous meningitis is s insidious that it may be two weeks before the parents realise that the illness i serious. At first there is merely lassitude, loss of interest in toys and in play unwillingness to talk, anorexia and constipation. Headache, at first sligh gradually becomes worse but meningeal signs may not appear until the thir week. In adults the malaise, headache and meningeal signs progress more rapidl though not as quickly as in acute pyogenic meningitis. There may be occasiona vomiting. The temperature is intermittently raised to 38° C. during the perio of ingravescence but remains raised, though rarely to high levels, once meningea signs appear. The condition then progresses more rapidly, and in untreated case cranial nerve palsies, hemiparesis or other signs of cerebral damage, hydrocephalus with drowsiness, coma and moderate papilloedema may occur. In miliary tuberculosis choroidal tubercles may be seen in the ocular fundi.

The CSF is under increased pressure. It is usually crystal clear or slightl turbid but, when allowed to stand, a fine clot forms like a cobweb. The flui contains up to 400 cells per cmm predominantly lymphocytes (the count mus be made on a fresh specimen before it forms a clot). There is slight rise in protei (60-100 mg per 100 ml) and a marked fall in glucose (below 50 mg per 100 ml) Detection of the tubercle bacillus in a smear of the centrifuged deposit fro the CSF may be difficult, the clot being the most likely place to find it Inoculation of CSF into a guinea-pig is valuable for confirming the diagnosi if this cannot be done from smears or cultures of the CSF but as the outcom will not be known for six weeks, treatment must be started without waitin for confirmation.

Diagnosis. As the ill effects of delayed treatment are so serious it is extremel important to diagnose tuberculous meningitis early. It should be considered especially in any patient known to have tuberculosis who develops a persisten headache, perhaps with slight pyrexia in the evening. If there is neck stiffnes or choroidal tubercles in the eye grounds there should be no hesitation in performing lumbar puncture and evidence of miliary tuberculosis should be sought by radiography of the chest. The differential diagnosis in the later stage is from other infections of the nervous system and is made largely upon the findings in the cerebrospinal fluid.

Treatment. As soon as the diagnosis is made, treatment should be started with the three standard antituberculosis drugs (p. 366). For the first fortnight of treatment isoniazid should also be given intrathecally in a dose of 0·5 mg/kg body weight to a maximum of 50 mg per day.

In all except patients with very early disease, prednisolone should be given by mouth, or intramuscularly, in a dose of 10 mg four times per day. If the lumbar puncture findings suggest spinal subarachnoid block, hydrocortisone hemisuccinate should be injected intrathecally every day, along with isoniazid, in a dose of 1 mg/kg body weight. If obstructive hydrocephalus develops in spite of treatment with corticosteroids, surgical methods for ensuring continuous ventricular drainage must be adopted. During the acute stage of the illness skilled nursing is essential, and measures must be taken to maintain adequate hydration and nutrition.

When the patient begins to recover, systemic and intrathecal treatment with corticosteroids can be withdrawn gradually and the doses of isoniazid can be reduced to the standard level (p. 367). Thereafter treatment continues along the lines described on page 368.

Prognosis. Untreated tuberculous meningitis is fatal in a few weeks but complete recovery is the rule with modern treatment if it is started before the appearance of focal signs or stupor. When treatment is started at a later stage the recovery rate is 60 per cent or less and the survivors may be mentally deficient, epileptic, deaf, blind or show some other permanent deficit.

Viral Meningitis

Viral infections of the central nervous system are often associated with meningitis (meningo-encephalitis, poliomyelitis, p. 867) but meningitis without clinical manifestation of parenchymal involvement of the nervous system may also occur. Some recognised clinical types are acute lymphocytic choriomeningitis and infection by ECHO or Coxsackie viruses. Meningitis may occur as a complication of viral infections primarily affecting other organs (mumps, p. 87; measles, p. 84; infectious mononucleosis, p. 745; psittacosis, p. 346; herpes zoster, p. 868 and infective hepatitis, p. 546).

In the absence of evidence of viral disease of other organs the various types of viral meningitis can only be differentiated by the virologist. Viral meningitis is the most common type now found in Britain.

ACUTE LYMPHOCYTIC CHORIOMENINGITIS

(*Benign Lymphocytic Meningitis*)

This type of meningitis occurs sporadically or in small epidemics.

Aetiology. The virus is believed to be endemic in house mice. It can sometimes be isolated from the CSF of patients and transmitted to mice. There is probably an initial viraemia, and pneumonia (p. 345) may be associated with meningitis.

Clinical Features. The condition commonly occurs in children and young adults. The onset is acute and evidence of meningeal irritation develops rapidly. Focal neurological signs are usually absent but diplopia and mild papilloedema may be observed. There may be a high pyrexia which gradually drops to normal in five to seven days. The CSF is under increased pressure. It is usually clear but may be turbid as there is an excess of lymphocytes (100-1,500 per cmm) which may persist long after clinical cure. There may be a slight increase in the protein but the sugar and chloride levels are normal.

Diagnosis. The diagnosis is from other forms of meningitis.

Pyogenic Meningitis. The turbid CSF contains an excess of polymorphonuclear leucocytes and the causative organism can be isolated.

Tuberculous Meningitis. This cause of lymphocytic meningitis may be difficult to diagnose owing to the technical difficulties of isolating the tubercle bacillus. A normal level of sugar in the CSF is in favour of a diagnosis of acute lymphocytic choriomeningitis. If there is any serious doubt as to the diagnosis, it is better to start treatment for tuberculous meningitis while awaiting further bacteriological reports.

Other Types of Viral Meningitis. Non-paralytic poliomyelitis may be impossible to differentiate. Signs of mumps, hepatitis, lymphadenopathy or other causes of viral meningitis may be present but the diagnosis may depend on serological tests.

Other Types of Meningitis. Canicola fever (p. 82), secondary syphilis, fungal and rarely carcinomatous involvement of the meninges may produce a similar picture of the CSF cytology which is characterised by a mononuclear cell proliferation.

Treatment. There is no specific treatment for the condition. The patient is kept at rest in bed on symptomatic treatment until the temperature has returned to normal.

Prognosis. Complete recovery is the rule in acute lymphocytic choriomeningitis.

Neurosyphilis

An old and frequently reiterated neurological aphorism says that neurosyphilis may mimic any neurological disease. As a corollary it is emphasised that neurosyphilis must be included in the differential diagnosis of all neurological problems and that a Wassermann reaction should be performed on all patients presenting with neural dysfunction.

Neurosyphilis may present as an acute or chronic process and may involve, singly or in combination, the meninges, blood vessels and parenchyma of brain and spinal cord. Though the clinical manifestations produced are diverse certain general observations are pertinent.

Pupillary abnormalities, described by Douglas Argyll Robertson, may accompany any neurosyphilitic clinical syndrome. The pupils are small, irregular and unequal. They do not react to light but respond to convergence and show an impaired response to mydriatics. The irises may be atrophied. In relatively few instances will all of these features be present. The complete picture of Argyll Robertson pupils is most frequently seen in tabes dorsalis and is distinctly uncommon in general paresis wherein some pupillary changes occur in about half of the cases. The observation of any discrepancy between the pupillary response to light and convergence even when other manifestations are lacking, should always suggest the possibility of neurosyphilis.

The *Wassermann reaction* is usually positive in neurosyphilis. In general paresis it is almost always so in both blood and cerebrospinal fluid, as it is in about 90 per cent of cases of meningovascular syphilis. In a fifth of tabetic patients, the Wassermann reaction in the CSF is negative and 10 per cent show negative serology in the blood. The FTA and TPI (p. 82) are more specific tests for the detection of neurosyphilis.

Examination of the CSF reveals abnormalities in the vast majority of cases of neurosyphilis. An increase in the cell count, usually lymphocytic and of moderate degree (10-100 per cmm) is almost invariably present when the disease is active. A moderate rise in the protein content is usual and the gamma globulin fraction thereof is often increased. Changes in the colloidal gold curve (p. 853) are frequent.

Meningovascular Syphilis

The essential lesion is endarteritis obliterans which may lead to arterial thrombosis and to the formation of a granuloma or gumma. The meninges may be covered by an exudate which damages cranial nerves. Lesions may predominantly affect arteries or meninges or both structures may be involved. Clinical manifestations usually occur within five years of the primary infection.

Intracranial Lesions. Occlusion of a cerebral artery may be due to syphilis which should be considered as a possibility in all cases of stroke, and particularly so when cerebral infarcts occur in young people.

Basal gummatous meningitis may present with cranial nerve palsies. Meningitis over the surface of the hemispheres may give rise to headaches and fits in addition to focal signs of cortical dysfunction. Rarely, a single large gumma may present as a slowly growing cerebral tumour.

Spinal Lesions. Thrombosis of the anterior spinal artery gives rise to lower motor neurone signs at the level of the lesion. Below the affected segments, pyramidal tract disturbance is usually manifest and there may also be impairment of pain and temperature sensation though the latter is often transient.

Thickening of the dura mater in the cervical region—called hypertrophic pachymeningitis—gives rise to lower motor neurone lesions in the arms and upper motor neurone lesions in the legs.

Meningitis accompanied by myelitis in the dorsal region causes 'girdle' pains and leads to progressive cord damage.

Parenchymal Disease

GENERAL PARALYSIS OF THE INSANE

The principal pathological changes are seen in the cortex. There is degeneration of cortical neurones giving rise to atrophy, particularly marked over the anterior part of the hemispheres. The meninges are thickened and infiltrated with lymphocytes.

General paralysis of the insane usually presents 5 to 15 years after the primary affection. Men are much more often affected than women.

Clinical Features. The initial and most characteristic feature is dementia, often of insidious onset and slow progression. Relatives or workmates usually first recognise the patient's intellectual deficit and later his deteriorating social adaptation. Delusions of grandeur occur only in a minority of cases. Signs of upper motor neurone lesions, usually bilateral and initially mild, are usually present and tremors of the head and lips are often manifest. Less common features include epileptic fits and transient episodes of focal cerebral disturbance such as hemiplegia, hemianopia or dysphasia.

TABES DORSALIS

The primary lesion is a degeneration of first order sensory neurones, central to the dorsal root ganglia, in the lower thoracic and lumbar nerve roots. Obvious macroscopic wasting affects the dorsal columns but all modalities of sensation may be impaired.

Males are more often affected than females, usually 5 to 20 years after the primary infection.

Clinical Features. Sensory disturbances are the most common initial symptoms. 'Lightning' pains of severe, lancinating nature occur in paroxysms. They may be localised to any part of the body but are most common in the legs. Pains radiating around the trunk in a 'girdle' distribution also occur. Paraesthesiae, likened to pins and needles, tingling or numbness often affect the feet.

Other disabilities may accompany these sensory manifestations or may be presenting features. Ataxia, of spinal type, due to proprioceptive loss is often prominent. Sphincter disturbance, particularly retention of urine, may be accompanied by impotence. Failing vision or diplopia may be symptoms. Perforating, painless ulcers of the feet and swollen, unstable joints (Charcot's joints) are sometimes found. Visceral crises may cause acute symptoms and the disturbance in function of a viscus may point to disease in the affected organ rather than in its innervation. Most common are gastric crises which give rise to abdominal pain and vomiting. Less common are laryngeal crises causing stridor, the strangury of vesical crises and tenesmus due to rectal crises.

The signs of tabes are mostly explicable on the basis of posterior root lesions. Tendon reflexes are lost, due to interruption of the reflex arcs, first at the ankles, then at the knees and later in the upper limbs; hypotonia with resultant hyperextensibility of the joints appears. The pain fibres are affected early with delay in or impairment of the response to pin prick over a characteristic distribution. The classical areas of loss are around the nose, the trunk from the angle of the sternum to the costal margin, the inner border of the forearms and the ring and little fingers, the perineum and the distal part of the lower limbs. Deep pain appreciation is also impaired so that the tendo calcaneus, calf muscles and testes become insensitive to pressure. Vibration and position sense in the feet are also lost early, but light touch is not affected until a later stage. The combination of loss of position sense and hypotonia gives rise to severe ataxia, so that the patient walks on a wide base lifting his feet high and stamping them down in an irregular and forceful manner. As vision compensates to some extent for the loss of proprioception, darkness or closure of the eyes aggravates the ataxia, hence Romberg's test (p. 805) is positive. Later, unsteadiness of the arms may also appear. The plantar responses remain flexor, but may be absent as a result of sensory loss.

Bilateral ptosis with compensatory wrinkling of the forehead and Argyll Robertson pupils constitute a typical tabetic facies. Less constant clinical manifestations also include pallor of the optic discs, defects in external ocular movement, distension of the bladder, and trophic changes such as ulcers or painless arthropathy.

Combined Neurosyphilitic Lesions

It is emphasised that the clinical syndromes outlined above represent only the commoner presentations of neurosyphilis. Combinations of pathological lesions also occur and give rise to mixed clinical pictures. Tabetic manifestations sometimes accompany those of general paralysis of the insane and the hybrid (taboparesis) may lead to cases of dementia accompanied by ataxia, lightning pains or areflexia; patients presenting with visceral crises may be found to have extensor plantar responses.

Treatment of Neurosyphilis

The essential part of the treatment of neurosyphilis of all types is the injection of procaine benzylpenicillin, 1 g daily for three weeks. The aim of treatment is to arrest the disease and restore the blood and CSF to normal. Further courses of penicillin must be given if (*a*) symptoms are not relieved or the picture continues to advance, (*b*) the CSF continues to show signs of active disease. The first abnormality to regress is the increase in cells but these may not return to normal until three months after treatment has been completed. The elevated protein takes longer to subside and the Lange curve may remain abnormal for as long as 12 months. The Wassermann reaction may never revert to normal. Lumbar puncture should be repeated at six-monthly intervals for two years and further courses of penicillin given so long as signs of activity remain. Evidence of clinical progression at any time is an indication for renewed treatment.

Viral Infections

Some viruses have a propensity for invasion of nerve cells and are called 'neurotropic'. The affinity may be specially marked for one type of nerve cell; the zoster variant of the varicella virus particularly involves sensory neurones and the anterior horn cells are vulnerable in poliomyelitis. Though these viruses most commonly invade their sites of predilection they may also sometimes involve the nervous system more widely; the virus of poliomyelitis often gives rise to a meningo-encephalitis and the zoster virus may rarely cause motor disability. Many viruses which usually cause diseases of other systems may sometimes implicate the nervous system. The many varieties of Coxsackie and echo viruses, which are common enteric pathogens, fairly often cause neurological disease as well as more widespread manifestations in other systems. The viruses of herpes simplex, mumps and infective hepatitis among many others, may occasionally invade the nervous system.

Some neurological diseases, of which encephalitis lethargica is one, are presumed to be of viral origin because of their epidemiological, clinical and pathological features though the causal agent has not been identified.

Neurological disorders are sometimes indirectly associated with viral diseases. In these instances abnormal immunological responses, evoked by the virus, cause damage to neural tissue without any viral invasion of neurones. The demyelinating encephalomyelitis (p. 872) which may follow any of the exanthemata is such an entity.

Slow Viral Infections

The acute or subacute neurological manifestations of viral infection have long been known. There has recently been much interest in the concept of 'slow' virus infections of the central nervous system causing chronic or relapsing neurological disease. Slow virus infections exhibit a long latent period (months or many years) between the initial infection and the subsequent clinical illness which once manifest, tends to run a protracted course. Two diseases of sheep, scrapie, an invariably fatal encephalopathy and visna, a demyelinating myelopathy, are proven examples of slow virus infections. Evidence for a similar cause of human disease is as yet scanty but there are suggestive findings.

A degeneration of grey matter, most marked in the cerebellum, causing a progressive ataxia, called kuru, is a disease which occurs naturally only in the members of one cannibalistic New Guinea tribe. The disease can, however, be transmitted to chimpanzees and there is much evidence to suggest that kuru is a slow virus infection transmitted by the eating of the infected brains of dead tribal members. The rare condition of spastic pseudosclerosis which is characterised by progressive dementia, epilepsy, extrapyramidal and motor neurone signs can also be transmitted from human sufferers to chimpanzees.

A slow virus infection has been adduced as a possible cause of a number of chronic neurological diseases, including motor neurone disease and disseminated sclerosis.

Encephalitis

This is a term which is sometimes confusing. Lesions of the brain due to toxins such as lead, to nutritional deficiencies or to degenerations of unknown cause, are best called encephalopathies. Encephalitis should be employed to denote infection and should, where possible, be defined by the type of infecting agent, as for instance suppurative encephalitis (p. 853). Difficulties arise about the classification of the immunologically-determined demyelinating lesions which may follow viral infections. It seems legitimate to use the traditional term of encephalitis or encephalomyelitis for these entities. The underlying pathogenesis of these conditions (acute disseminated encephalomyelitis, p. 872) differs from the direct viral invasion of brain cells discussed below. The distinction between demyelinating encephalitis and viral encephalitis is sometimes difficult or impossible to make on clinical grounds but the implications for treatment and prognosis in the two conditions are different.

Viral Encephalitis

All of the viruses which cause meningitis (p. 859) may also give rise to an encephalitis. Encephalitic features may predominate or a combined picture of meningo-encephalitis may occur. More specific types of virus encephalitis occur in epidemic or sporadic forms. The severe arthropod-borne epidemic types such as Japanese-B or equine encephalitis occur in Japan, the United States, Russia and the Far East but are almost unknown in Britain. Sporadic causes occur fairly commonly but often the causative virus is not isolated though influenza and herpes simplex viruses are fairly frequently implicated.

Pathology. The distribution and extent of lesions vary to some extent with the type of infecting virus. There is usually diffuse damage to cells in the cortex, basal ganglia and brain stem. Inclusion bodies are often present in neurones and glial cells. There is usually infiltration between neurones and in the perivascular spaces by polymorphonuclear cells initially and later by lymphocytes and mononuclear cells. There is accompanying neuroglial proliferation. Herpes simplex encephalitis tends particularly to affect the temporal lobes and in encephalitis lethargica the substantia nigra, mid brain and basal ganglia are most prominently involved.

Clinical Features. An acute onset of headache, often accompanied by fever, is the usual clinical presentation common to all types of viral encephalitis. Disturbance of consciousness, varying from mild drowsiness to deep coma, usually supervenes early and may sometimes advance dramatically. Epilepsy of focal or generalised type is common. A variety of focal signs such as aphasia, hemi- or tetraplegia, cranial nerve palsies and sensory disturbances may occur but sometimes there are none. The clinical features rarely enable a firm diagnosis of the causal agent to be made but some types of encephalitis present distinctive facets.

HERPES SIMPLEX ENCEPHALITIS. The onset is usually acute and commonly is marked by behavioural disturbance and a confusional state resembling a psychosis. This often lasts two or three days before other features develop. Fits are very common. Papilloedema and variable focal neurological signs may be present. Progression over a few days to coma is common.

BRAIN-STEM ENCEPHALITIS. This is presumed to be of viral origin but the causal agent has not been defined. There is usually an antecedent history of mild upper respiratory infection. The onset, attended by headache, is often marked by double vision and dysarthria. Later there is increasing drowsiness and progressive cranial nerve involvement.

ENCEPHALITIS LETHARGICA. This occurred in epidemic form during the 1920's. Its present incidence is difficult to determine. Some believe that it has disappeared but there is evidence that sporadic cases still occur. The illness varies markedly in severity. Headache and double vision may be the only features but sleep disturbances, respiratory tics, pyramidal and extrapyramidal signs may be manifest. Oculogyric crises or Parkinsonism may develop during the early stages of the illness or may be a sequel.

BENIGN MYALGIC ENCEPHALOMYELITIS. This is a condition which is presumed, though not proven, to be of viral origin. It occurs in closed communities such as schools and hospitals. It presents with pyrexia and diffuse muscle pains, tremors and marked mood disturbances which may recur over long periods.

SUBACUTE SCLEROSING PANENCEPHALITIS. This condition is now thought to be due to infection by a myxovirus which is either measles virus or a closely related agent. It occurs in children and adolescents. The onset is usually an insidious intellectual deterioration, apathy and clumsiness accompanied later by myoclonic jerks and other involuntary movements. As the disease progresses rigidity and dementia supervene.

RABIES. This presents a distinctive clinical picture described on page 972.

Diagnosis. These various forms of viral encephalitis should first be distinguished from other intracranial diseases such as cerebral tumour or abscess and thereafter the type of viral infection should, if possible, be determined. The differential diagnosis depends on the nature of the clinical features and the attendant circumstances. When the predominant features are progressive, focal affection of one hemisphere accompanied by headache and drowsiness the picture may strongly suggest a space-occupying lesion and intensive investigation may be needed to exclude such conditions as cerebral abscess. When the illness is mild, neurological signs indefinite and there are attendant general signs of viral infection the diagnosis will often be made presumptively after the patient improves.

Investigations are more helpful in excluding other lesions than in confirming the diagnosis of viral encephalitis. In a minority of instances the CSF is normal. Usually the CSF pressure and protein content are moderately raised and there is a lymphocytic pleocytosis. The sugar content is normal. The EEG is usually altered. There is a diffuse slowing of the rhythms but the findings are non-specific. In subacute sclerosing panencephalitis the EEG is distinctive, showing bursts of triphasic slow waves. Occasionally in herpes simplex encephalitis a radioactive cerebral scan will show areas of increased uptake in one or both temporal lobes.

Serological tests and culture may identify the infecting virus but the results of such tests are usually available too late to guide treatment.

Herpes simplex encephalitis is potentially treatable so that it is important to establish this diagnosis when the patient's illness is severe and progressive. In such circumstances a surgical biopsy of the temporal lobe may be justified to demonstrate the presence of this infecting agent.

Treatment. The management of most cases of viral encephalitis consists of nursing care and the prevention of intercurrent infections. When a positive diagnosis of herpes simplex encephalitis has been made, idoxuridine (p. 105) may be given intravenously; the total dose is 500 mg/kg and this should be given slowly in equally divided doses over five successive days.

Prognosis. This is highly variable. Most patients survive and may recover completely but persisting focal defects are frequent. A significant number (perhaps 10-30 per cent) die. The outlook is particularly poor in herpes simplex encephalitis and in subacute sclerosing panencephalitis. Brain-stem encephalitis has a good prognosis; complete, if sometimes slow, recovery is almost invariable.

Acute Anterior Poliomyelitis

Aetiology. The disease is caused by one of three related polioviruses which comprise a subdivision of the group of enteroviruses. It is becoming much less common following the widespread use of prophylactic immunisation by oral vaccines (p. 59). Infection usually occurs through the nasopharynx.

Pathology. The virus is particularly liable to affect the grey matter of spinal cord, brain stem and cortex and has a particular propensity to damage anterior horn cells especially those within the lumbar segments. There is often accompanying infiltration of the meninges with lymphocytes.

Clinical Features. The incubation period is 7-14 days. At the onset there is usually mild pyrexia and headache which improves after a few days. Many cases do not progress beyond this stage. In other instances, after a period of well-being lasting approximately a week there is a recurrence of pyrexia and headache accompanied by neck stiffness and signs of meningeal irritation. Paralysis may occur later. The extent is variable. Weakness of one muscle group may progress to widespread paresis. Respiratory failure may supervene if intercostal muscles are paralysed or the medullary motor nuclei are involved.

The CSF shows a lymphocytic pleocytosis, a rise in protein and a normal sugar content.

Treatment. In the early stages bed rest is imperative. At the onset of respiratory difficulties a tracheostomy should be performed and intermittent positive respiration instituted.

Prognosis. Epidemics vary widely in their incidence of abortive and non-paralytic cases and in mortality rate. Death occurs from respiratory paralysis. Paralysis is greatest at the end of the first week of the major illness. Gradual recovery may then take place for several months but any muscle showing no signs of recovery by the end of a month will not regain useful function. It is difficult to make a more definite prediction about the extent of permanent disability until three to six months after the onset. Second attacks are very rare.

Herpes Zoster

(SHINGLES)

Viral invasion of posterior root ganglia causes pain followed by a rash over the cutaneous distribution of the affected nerve root. The virus is the same as that causing chickenpox, and contacts with one disease may develop the other. In herpes zoster there is a high level of specific antibody in the blood, and this is believed to indicate re-activation of a previous infection by chickenpox virus which has lain dormant in the body. The virus occasionally invades the spinal cord or the brain, giving rise to myelitis or encephalitis. It sometimes involves nerve roots which are the site of another pathological process such as neuroma, metastatic tumours, Hodgkin's disease and leukaemia.

Clinical Features. The first symptom is usually severe continuous pain in the distribution of the affected nerve root. There is often little systemic upset but malaise and pyrexia may accompany the pain, especially in old age. After three or four days the skin in the affected area becomes reddened and vesicles appear. The vesicles dry up over the course of five or six days leaving small scars. The affected dermatomes may be permanently anaesthetic. Scarring is more severe if the vesicles are secondarily infected.

Any dorsal root ganglion may be infected, most commonly those supplying the trunk where two or three adjacent dermatomes on one side only are often involved. Infection of the trigeminal ganglion usually involves the ophthalmic division; the vesicles appear on the cornea and may lead to corneal ulceration with the danger of resultant scarring and impairment of vision (ophthalmic herpes).

The pain of herpes zoster usually subsides as the eruption fades, but occasionally, especially in old people, it may be followed by a persistent and intractable post-herpetic neuralgia which may last for months or years. Segmental muscle wasting may occur sometimes. It may result from involvement of the motor root in the inflammatory reaction, but it is often delayed until a month after the sensory signs, suggesting a delayed allergic reaction. Facial palsy may be caused by infection of the geniculate ganglion (geniculate herpes) spreading to the trunk of the facial nerve, and occasionally also to the eighth nerve causing deafness or vertigo. Herpetic vesicles may be seen on the auditory meatus and soft palate.

Diagnosis. Herpes zoster is easily recognised when the rash has appeared but, in the antecedent painful stage before development of the rash, it is frequently misdiagnosed as pleurisy, cholecystitis or a spinal cord lesion. It is important to remember the possibility that herpes zoster may be associated with an underlying lesion of the dorsal root ganglia due to organic disease.

Treatment. Cytarabine (p. 105) may be used in severe or complicated cases. The vesicles should be kept dry with talcum powder or may be covered with collodion. An ointment containing such local anaesthetic as ung. cinchocain co. BPC applied to the site of the rash gives great relief in the acute stage. Analgesics may also be required. Antibiotics may be needed if secondary infection becomes severe.

The treatment of post-herpetic neuralgia is difficult. Analgesics should be continued, but the more dangerous ones, such as morphine, should be avoided because of the risk of addiction. Radiotherapy to the affected root may be advised if the pain proves intractable. Section of the nerve or nerve root is never successful but in suitable cases section of the spinothalamic tract may be carried out with benefit.

DEMYELINATING DISEASES

Loss of myelin sheaths occurs with many disorders of the central and peripheral nervous systems but there is a particular category with certain clinical and pathological features in common in which loss of myelin is considered to be the primary change and the axis cylinders may be spared or, if affected, are damaged secondarily. The lesions are almost entirely confined to the white matter of the central nervous system. They are initially inflammatory in type but differ from lesions known to be caused by direct viral infection and so they are grouped separately from viral encephalomyelitis (p. 865). Their nature is uncertain but there are reasons for considering that they may be caused by an auto-immune process which damages the myelin-forming cells, the oligodendrocytes.

Disseminated Sclerosis

(MULTIPLE SCLEROSIS)

In the Northern hemisphere this is the most common disease of the nervous system, affecting people from 20 to 50 years of age with maximum incidence in young adults.

Aetiology. The cause is unknown. Six per cent of patients have affected relatives, suggesting that genetic factors are contributory. The initial attack and later relapses may be precipitated by unusual fatigue, trauma, infection, severe cold and allergic reactions.

Pathology. The acute lesion consists of a circumscribed area in which the myelin sheaths have undergone destruction while the axis cylinders show only irregular swelling. The plaque has a swollen pinkish appearance as blood vessels are dilated but there is little infiltration with inflammatory cells. Reactive gliosis follows, so that the chronic lesion becomes a glial scar with a shrunken greyish appearance. The lesions are widely scattered in the white matter of the brain, especially round the ventricles, in the spinal cord, and in the optic nerves. Despite the disseminated distribution there is a tendency for spinal cord and brain stem lesions to occur in symmetrical situations.

Clinical Features. The most characteristic features are the relapsing and remitting course of the disease and the widespread lesions which result in a multiple symptomatology. These features rather than any combination or pattern of symptoms and signs enable the diagnosis to be made. The clinical features depend on the sites of plaques which may occur in any part of the white matter, but there is a predilection for certain sites which enables some clinical patterns to be distinguished. The acute lesion causes temporary functional interruption of fibres which are not permanently damaged, so the early symptoms often tend to improve. The initial clinical feature develops fairly suddenly and disappears after a few days or weeks. It may be any one of the many associated with this disease but two are particularly common. In young people retrobulbar neuritis is probably the lesion which is produced first most frequently, while over the age of 50 weakness of one or both lower limbs is usually the presenting symptom.

Retrobulbar neuritis causes blurring or loss of the vision of one eye. There may be pain on movement of the eyeball. The optic disc is normal at this stage but there is a large central scotoma in the visual field of the affected eye and direct and consensual light reflexes are reduced when that eye is illuminated. Rarely, when the plaque lies immediately behind the nerve head ('papillitis'), a mild degree of swelling of the disc may be seen. The vision recovers after two to three weeks, though a partial central scotoma may persist, and pallor of the temporal half of the disc may subsequently appear.

Weakness, heaviness or stiffness of one or both limbs due to corticospinal tract demyelination develops fairly suddenly. It may be so slight as to cause little disability or it may be crippling for a few days or weeks. Spontaneous jerks of the legs while at rest are common in the early stage.

Other symptoms which may be the initial ones or occur during relapses are due to plaques in the brain stem, cerebellum or spinal cord. Common brain stem symptoms are transient diplopia, often unaccompanied by any observable strabismus, and acute vertigo with vomiting. Cerebellar lesions cause incoordination of an arm (with intention tremor, ataxia of gait or dysarthria). Transient unsteadiness of an arm or leg may also be due to impaired proprioception. This may render the limb 'useless' though it is not paralysed. Posterior column involvement in the cervical region may cause sudden electric shock-like feelings in the arms or legs when the neck is flexed. Spinothalamic tract lesions cause numbness or paraesthesiae in the face, trunk, or limbs often described as being like a tight band round the limb. Transient disturbances of bladder function such as urgency, precipitancy or hesitancy of micturition (often labelled cystitis) may occur at an early stage as may impotence.

Examination usually reveals slight but definite signs of organic disease. Pallor of the temporal half of one or both optic discs is common even though the patient may never have been aware of visual disturbance. Nystagmus of ataxic or cerebellar type (p. 818), intention tremor, and corticospinal tract signs such as extensor plantar responses, muscle weakness and increase in reflexes and tone are common. Vibration sense is frequently diminished and impairment of the sense of passive movement may also be found. Analgesia or loss of sensation of light touch may be found but rarely persists. Most of these signs recede, but the changes in the optic disc are permanent, and often the abdominal reflexes become fatiguable then disappear permanently.

After the initial attack, there may be an interval of months or years before the second episode occurs which may be characterised by a recurrence of previous clinical features or, more likely, the development of new ones. The later course may be one of relapses and remissions with cumulative neurological defects, or there may be slowly progressive damage of the spinal cord simulating the picture of compression. The progressive course most often occurs when the disease starts in middle age. The course of either type eventually results in permanent disability in which the predominant features may be a spastic paraplegia or tetraplegia with incontinence, gross cerebellar disturbance with an ataxic gait, or mixed signs of widespread lesions. Mental changes may occur such as a failure to appreciate the seriousness of the condition (euphoria) but, although it may be an early feature, it is by no means pathognomonic of disseminated sclerosis.

Abnormalities of the CSF are present in at least half of the cases. A mild lymphocytosis amounting to 10 or 15 cells per cmm or a slight rise in protein rarely exceeding 80 mg per 100 ml may be present and increased proportion of gamma globulin is common. A characteristic feature is a disturbance of the Lange colloidal gold curve (p. 853). The most common abnormality is a first zone rise, but a mid-zone rise and non-specific changes also occur. The combination of a paretic curve with a negative Wassermann reaction is very suggestive of disseminated sclerosis. The CSF changes do not appear to correlate with the stage or degree of activity of the disease.

Diagnosis. There is no clinical feature or test which is pathognomonic of disseminated sclerosis, which may simulate almost any disease of the nervous system. The diagnosis depends on the demonstration of signs indicating multiple lesions and on a history of relapse and remission. Thus the diagnosis may be suspected but cannot be made with certainty after a single episode of demyelination. Sometimes, as outlined above, the course of disseminated sclerosis is progressive and the lesion apparently confined to one area in the spinal cord. Finally, it is emphasised that remissions may occur in other neurological diseases, such as neurosyphilis. In some cases, therefore, the diagnosis of disseminated sclerosis is achieved by a process of exclusion. It is important in all cases where it is the suspected diagnosis to eliminate potentially curable conditions. The appropriate investigations and the lengths to which these should be pursued depend on the particular clinical syndrome presented. In cases of slowly progressive spastic paraparesis a myelogram may be needed to exclude compression of the spinal cord. Syphilis should always be eliminated and the possibility of vitamin B_{12} deficiency will sometimes need to be explored.

Treatment. There is no specific treatment but a great deal can be done to help the patient. An acute relapse may respond to a high-dosage course of ACTH. During a relapse the patient should be confined to bed but the period of rest must be reduced to a minimum as coordination is lost rapidly. A regime of regulated activity is essential, avoiding over-fatigue on the one hand and inactivity on the other. Relapses are often due to urinary or other infections. Successful treatment may result in remission of the neurological symptoms.

Well planned physiotherapy and occupational therapy are of great value. Passive movement will relieve spasticity and exercises to improve coordination will help to overcome ataxia. Drugs such as atropine and ephedrine are useful for precipitancy of micturition, and carbachol may be used if there is severe hesitancy or retention of urine. The psychological aspect must not be neglected. An attitude of reasoned optimism and encouragement is helpful and to be preferred to concealment of the true state of affairs or the prescription of useless remedies. Orthopaedic appliances and a wheel-chair may make life quite tolerable for the disabled person.

Prognosis. Recovery from the current attack may reasonably be expected but it is impossible to forecast the next relapse. The time elapsing between the first and second episodes is a useful pointer to the subsequent course. If a second attack occurs in less than a year from the first the course is likely to be progressive. If a considerably longer free period is present the prognosis is so much the better and improves with every year that passes. Some patients have no further attacks, especially if the initial lesion is retrobulbar neuritis, so the picture is not one of unrelieved gloom. The spinal type often progresses extremely slowly and, even at a late stage, is compatible with a wheel-chair life. Brain stem involvement carries a worse prognosis. The most disabling lesion is ataxia. Although some cases progress rapidly, 60 per cent are without disability five years after the onset of symptoms and 40 per cent after 10 years. The average duration of life is at least 20 years from the onset. Death is usually caused by urinary infection, pneumonia or pressure sores.

Acute Demyelinating Encephalomyelitis

(ACUTE DISSEMINATED ENCEPHALOMYELITIS)

This is a group of related acute disorders occurring without obvious cause or following an upper respiratory infection and certain infectious diseases such as measles and chickenpox or after vaccination. The pathology is probably due to a sensitivity reaction. There are widespread areas of perivenous demyelination throughout the brain and spinal cord.

Clinical Features. The time of onset varies with the different infectious diseases; in measles it is the 4th to the 6th day, and in chickenpox the 5th to the 12th day of the illness. The disease appears on the 10th to the 12th day after vaccination. Headache, vomiting, pyrexia and delirium are common presenting features and signs of meningeal irritation may also be found. Fits or coma may occur. Flaccid paralysis and extensor plantar responses are common but sensory loss is unusual. Cerebellar signs may be present especially when the disorder follows chickenpox. Retention of urine is also a frequent manifestation.

The CSF may be normal or show a small increase of mononuclear cells and protein. The Lange curve shows no characteristic pattern.

Neuromyelitis optica is a restricted form of the disease characterised by massive demyelination of the spinal cord and both optic nerves, usually following an upper respiratory infection. Either the optic or the spinal lesion may occur first but they may develop simultaneously.

Diagnosis. When the features of an acute encephalitis occur in association with one of the exanthemata or following vaccination the diagnosis should be easy but in cryptogenic cases other causes of 'encephalitis' must be excluded (p. 864). It may be impossible to distinguish acute disseminated encephalomyelitis (or especially neuromyelitis optica) from acute disseminated sclerosis until the passage of time has shown that remissions and relapses do not occur. Syphilitic myelitis is distinguished by the serological reactions.

Treatment. ACTH 80-120 units by injection or prednisone 60 mg by mouth daily for several days followed by a maintenance dose for two to three weeks is beneficial. These drugs must be used with caution in chickenpox if encephalitis develops before the rash has subsided as the rash may become confluent and haemorrhagic. The usual care of the paralysed and incontinent patient is required (p. 889).

Prognosis. The mortality rate is high in neuromyelitis optica and in post-vaccinal encephalomyelitis but is low in the post-exanthematous cases. If the patient survives, the recovery may be remarkably complete and second attacks are very rare.

DISORDERS OF THE EXTRAPYRAMIDAL SYSTEM

In disorders of this system voluntary movement is disturbed, involuntary movements appear and muscle tone is altered.

Parkinsonism

Aetiology. Parkinsonism is the name given to a clinical syndrome, comprising impairment of movement (hypokinesis), rigidity and tremor, which results from damage to the basal ganglia. This clinical picture is common to a number of conditions, namely:

Paralysis Agitans. This is the largest single category. The basal ganglia are involved in a degenerative process whose cause is unknown.

Post-encephalitic Parkinsonism. This is a sequel to an attack of encephalitis lethargica (p. 866).

Atherosclerotic Parkinsonism. Cerebrovascular disease may affect the basal ganglia and lead to features of Parkinsonism.

Toxic Causes. The syndrome of Parkinsonism may arise as a result of (1) ingestion of drugs particularly phenothiazines; (2) from deposition of copper in the basal ganglia in Wilson's disease (p. 876); (3) from poisoning by manganese, mercury or carbon monoxide.

Miscellaneous Causes. Rarer causes of Parkinsonism include trauma, syphili and cerebral tumour.

Pathology. The most consistent histological change found in Parkinsonism, whatever the cause, is cellular loss and depigmentation in the substantia nigra This is accompanied by biochemical changes, notably in the corpus striatum wherein there is a diminution of dopamine. The substantia nigra, corpus striatum and globus pallidus are interconnected by systems of fibres, one of which uses dopamine as a transmitter substance and the other utilises acetylcholine in this role. It seems likely that in Parkinsonism there is an imbalance between these two systems; dopaminergic activity is reduced and this results in hypokinesis; the cholinergic system is relatively over-active and this causes the 'positive features of tremor and rigidity.

Post-encephalitic Parkinsonism is due to a destruction by a virus of the pigment-bearing cells in the substantia nigra, with lymphocytic infiltration, perivascular cuffing and glial reaction. In paralysis agitans there is degeneration of some of the cells of the basal ganglia, particularly in the globus pallidus, without evidence of inflammatory or vascular changes. In cases due to atherosclerosis the vascular changes are prominent, and secondary degeneration of neurones and cellular necrosis occur. These changes are not confined to extrapyramidal neurones and usually involve the adjacent internal capsule.

Clinical Features. Paralysis agitans may be taken as the prototype of Parkinsonism and the difference between it and the other types is described on page 875.

PARALYSIS AGITANS. The onset of this disorder is commonly in the 50 to 60 age group. The first sign is usually tremor of one hand. It is a coarse, regular, rhythmical tremor 4 to 8 times per second, between opposing groups of muscles such as flexion-extension or pronation-supination at the wrist, or abduction-adduction of the thumb. It is most marked in the distal parts of the limbs. It usually starts in one upper limb, spreading after months or years to the other or to the lower limbs. The tongue and closed eyelids may also be tremulous. The tremor of Parkinsonism is present at rest, disappears during a voluntary movement but may reappear when the limb holds a new posture.

Poverty of movement and rigidity follow soon after tremor. The face loses its movements of expression and the unblinking stare gives a false impression of idiocy. Automatic movements such as swinging the arms when walking are reduced or lost and if the patient trips he does not make the reflex movements necessary to preserve his balance. The gait is composed of small shuffling steps and is often more of a run than a walk. There is no weakness but all movements are infrequent and slow except speech which is rapid and monotonous with slurring of consonants and repetition of syllables. Handwriting is cramped and tends to become progressively smaller. Nevertheless with concentrated effort, movement, speech and writing can often be performed in a normal manner for a few moments, but rapidly return to their former level when attention is relaxed.

Rigidity is of extrapyramidal type. It is usually of the 'cog-wheel' variety

p. 799), increased by voluntary contraction of the opposite limb. The muscles of the trunk are also rigid, with slight flexion of the trunk and limbs and restricted rotary movement of the spine. The fingers are held flexed at the metacarpophalangeal joints but extended at the interphalangeal joints with adduction of he thumb. There is no sensory loss and in general the tendon jerks are not altered. Cramp or muscle pain is quite common.

POST-ENCEPHALITIC PARKINSONISM. This may appear at any age. Tremor is ess prominent than in paralysis agitans but rigidity is a marked feature. Other differences are the disturbances of ocular innervation and the more obvious signs of hypothalamic damage, such as hypersalivation or excess sebaceous secretion. Sleep disturbance and behaviour disorders rarely persist.

Various pupillary abnormalities occur but the most common is failure of the convergence reflex associated with deficient ocular convergence. Oculogyric crises may occur in which there is forced upward deviation of the eyes for minutes or hours.

ATHEROSCLEROTIC PARKINSONISM. The age of onset may be later than paralysis agitans and rigidity is more marked than tremor. Neighbouring tracts are commonly involved in the ischaemic area so that extensor plantar reflexes may be found in this type.

Diagnosis. When the three elements of tremor, rigidity and hypokinesis are present the diagnosis is usually obvious. Where tremor is the predominant feature the characteristics outlined above will serve to differentiate Parkinsonian tremor from the more rapid, usually fine, tremors of thyrotoxicosis, alcoholism and so-called senile tremor. Familial tremor too is usually more rapid, may begin early in life and is not accompanied by rigidity or impairment of movement; as the name implies there is usually a family history of similar movements.

Treatment. The underlying cause of Parkinsonism should be treated when possible. Discontinuance of a causative drug is the only common remediable factor.

The long established treatment of Parkinsonism is based on the use of anticholinergic drugs. Originally, mixtures of belladonna alkaloids were used but these have now largely been supplanted by synthetic preparations, such as benzhexol hydrochloride (2 mg or 5 mg tablets), benztropine (2 mg tablets) and orphenadrine (50 mg tablets). One of these drugs is introduced in small amounts, such as one tablet twice daily, and the dose is increased until toxic effects of dryness of the mouth or blurring of vision supervene. The dose is then reduced slightly to obviate these effects. Anticholinergic drugs do produce improvement in Parkinsonism but this is rarely of marked degree.

More recently Parkinsonism has been treated by increasing the level of cerebral dopamine. Levodopa (L-dopa) is the drug employed for this purpose. Given by mouth, in doses ranging from 2 to 8 g daily, levodopa produces significant improvement in many patients. Hypokinesis is particularly helped. Side-effects, notably vomiting, induced involuntary movements and postural hypotension, are common. The duration of the beneficial effects of this drug and its influence on the natural history of the disease are not yet determined.

Other drugs such as amantadine and dopa-decarboxylase inhibitors have also been used in the treatment of Parkinsonism, and further therapeutic advances are to be expected; at present the most effective treatment comprises a combination of an anticholinergic drug and levodopa.

Since the introduction of treatment with levodopa the indications for the surgical treatment of Parkinsonism have become less clear-cut. Stereotactic destruction of the ventrolateral nucleus of the thalamus or the globus pallidus usually produces improvement in tremor and rigidity. These operations, however, rarely help hypokinesis and sometimes may aggravate this very disabling aspect of the disease. In a patient who is young and whose principal disability is tremor with little akinesis, operation should still be considered.

Prognosis. This depends on the cause. Paralysis agitans and atherosclerotic Parkinsonism tend to progress but the rate may be slow or rapid. Post-encephalitic Parkinsonism does not change much from year to year.

Hepato-lenticular Degeneration

(WILSON'S DISEASE)

Wilson's disease is a rare hereditary disorder of copper metabolism.

Aetiology. Copper is normally absorbed in small amounts from the gut as a loose complex with albumin and carried to the liver. There some of it is re-excreted in the bile but a fraction enters the general circulation. In the liver some of the blood copper is transferred to globulin to which it is more firmly bound, forming caeruloplasmin. This copper-globulin is an oxidase enzyme but its physiological role is unknown.

In Wilson's disease copper is absorbed in excess but the transfer from the albumin-bound to the globulin-bound complex is defective, thus the serum caeruloplasmin level is low. Some of the extra copper absorbed is excreted in the urine while the rest is deposited in the tissues, particularly in the brain, liver, kidney and in Descemet's membrane in the eye. These organs may be damaged either by enzymatic poisoning by the heavy metal or by cellular necrosis followed by fibrosis (or gliosis in the brain).

The metabolic abnormality is inherited as an autosomal recessive characteristic; thus it occurs in either sex but is rare because both parents must carry the abnormal gene (p. 7). In practice this is most probable if the parents are related.

Clinical Features. The biochemical abnormality of Wilson's disease is present from birth, but clinical evidence does not appear until adolescence. There are two main clinical types depending on whether the hepatic or cerebral signs are more evident.

Hepatic Type. There is progressive hepatic cirrhosis of a coarse nodular type, leading gradually to portal hypertension and eventually to hepatic failure pp. 558-560). Juvenile cirrhosis should always suggest the possibility of Wilson's disease. Jaundice may precede it. It is sometimes haemolytic in type.

Cerebral Type. Necrosis and sclerosis of the corpus striatum cause basal ganglion syndromes in adolescence (p. 798). Most common is choreo-athetosis, but Parkinsonism may be caused according to the site mainly affected. There is usually cortical involvement leading to progressive dementia in which loss of emotional control is a feature.

Copper deposition in Descemet's membrane of the eye causes a golden-brown, yellow or green ring round the cornea. This Kayser-Fleischer ring, as it is called, appears in both types and is pathognomonic of Wilson's disease.

The urine contains excess copper and often excess amino acids (without any specific pattern). Renal tubular damage by copper may upset excretion of uric acid, sugar, phosphates, etc., but it is not certain whether aminoaciduria is caused in this way or whether it is an independent biochemical defect. Caeruloplasmin (measured as serum copper oxidase) is deficient in the blood.

Differential Diagnosis. The hepatic type must be differentiated from other causes of juvenile cirrhosis (pp. 557, 567). The cerebral type is likely to be confused with congenital disorders of the basal ganglia, kernicterus (p. 879) or post-encephalitic Parkinsonism (p. 875). The Kayser-Fleischer ring and the biochemical abnormalities are diagnostic.

Treatment. This disorder was previously progressive and fatal within a few years after the appearance of clinical signs. It can now be arrested by giving copper-binding drugs (chelating agents) which mobilise copper from the tissues and promote its excretion in the urine. The most valuable of these is penicillamine, 300 mg. t.d.s. orally. If it is not available or too expensive, dimercaprol (BAL) or disodium calcium versenate may be given but either is a less satisfactory substitute. Hepatic and cerebral symptoms are treated symptomatically with diet and anti-Parkinsonism drugs.

Siblings should be examined as clinical or biochemical evidence of Wilson's disease may be detected at a stage where treatment, if started promptly and continued throughout life, may prevent the appearance or progression of clinical features.

Sydenham's Chorea

(ST VITUS' DANCE)

This is a disease of children characterised by involuntary movements.

Aetiology. Chorea is associated with rheumatic fever though the exact nature of the association is uncertain. Arthritis is absent and only a small percentage of patients with chorea have active carditis. Chorea generally occurs between the ages of 5 and 15 and girls are affected three times more often than boys. Mental stress may also play a part and is certainly a common precipitating factor. Chorea occurs occasionally during pregnancy in young women (chorea gravidarum).

Pathology. There is generalised oedema and congestion of the brain, mos evident in the basal ganglia but also involving the cerebral cortex. Inflammator cells are few but there is diffuse degeneration of neurones.

Clinical Features. The onset may be insidious, with fidgety movement gradually becoming more violent, or it may be sudden after an emotiona disturbance. The movements are irregular, non-repetitive and present at rest but intensified during voluntary movement which is thus made irregular and jerky. They are absent during sleep. The movements may be quasi-purposive or just a series of sudden twitches involving several muscles simultaneously. All limbs and often the face and tongue may be involved. Restless grimacing of the face and inability to maintain the tongue in a protruded position are common features and the tongue movements may interfere with speech and swallowing. Respiration may also be irregular and jerky.

Associated movements are also disturbed by exaggeration or incoordination. Thus if the patient, while grasping the examiner's hand, is asked to protrude his tongue or clench the other fist, irregular contractions of the hand will be felt. Tone is greatly reduced so that hyperextensibility of the joints can be demonstrated. If the hands are held forward, palms down, they assume a typical posture of flexion at the wrist and hyperextension at all the finger joints. There is often hyperpronation of the arms if they are held above the head. The hypotonia also causes the reflexes to be difficult to elicit, but when obtained they show a characteristic sustained contraction. The plantar responses are flexor and there is no sensory loss. The CSF is normal. There is usually no pyrexia and the ESR is normal. If there is fever or a raised ESR it is likely that active carditis is present.

Diagnosis. This is not difficult. In habit spasm (tic) the pattern of involuntary movement is repeated with little variation; in athetosis the movements are more slow and sinuous. Huntington's chorea occurs in middle age in patients with dementia and there is usually a family history to be obtained.

Treatment. Complete bed rest and quiet are essential for at least a month and it may be necessary to remove the child to hospital to obtain this. The sides of the cot or bed should be padded to avoid injury. Skin abrasion must also be prevented. When swallowing is affected, feeding by gastric tube is necessary. There is no specific drug treatment but sedatives such as phenobarbitone or tranquillising drugs may be useful for the control of restlessness.

Prognosis. Death is very rare; most cases recover in 6 to 12 weeks. Second attacks occur in a third of cases and repeated attacks are not uncommon. This increases the possibility of occurrence of rheumatic carditis.

Huntington's Chorea

This is a good example of a human disease inherited as a Mendelian dominant of autosomal type (p. 7). Sporadic cases may occur. Its incidence is about 6 per 100,000 of the population but because of its familial nature its local incidence may be much greater. The first signs usually appear between the ages of 30 and 45. These are usually choreiform movements which are faster, more jerky and altogether more bizarre than Sydenham's chorea. Subsequently dementia develops and progresses to a state of complete incapacity requiring admission to a mental hospital in 10 to 15 years. Occasionally dementia may precede the involuntary movements. The EEG shows a low voltage, featureless type of record which differs from that found in other types of dementia.

Diagnosis. *Sydenham's chorea* occurs at an earlier age. There is no dementia and usually no family history. The course is not progressive.

Multiple tics occurring in hysterical individuals may be very difficult to differentiate. There is no dementia and no family history.

Pre-senile dementia (p. 941) of other types may require consideration in the rare cases where dementia precedes Huntington's chorea.

Cerebral atherosclerosis may cause both dementia and chorea but occurs at a later age and without a family history.

Treatment. There is no specific treatment but thiopropazate or tetrabenazine may help to control the involuntary movements.

Athetosis

This is characterised by unilateral or bilateral involuntary movements.

Pathology. The lesion is in the putamen. Most cases are congenital, being due to a primary disorder of myelination of striatal neurones, with glial formation, developing in intrauterine life. It may also be caused by cerebral anoxia at birth or by kernicterus (p. 880). In childhood it may occur as a result of damage to the basal ganglia during the exanthematous diseases, in adolescence from Wilson's disease and in the elderly from cerebrovascular disease. The lesions are usually bilateral.

Clinical Features. The slow, sinuous writhing movements ('mobile spasm') affect the distal parts of the limbs more than the proximal. The facial muscles are also affected by grimacing. In congenital cases abnormal movements are seldom noted until several months after birth. Movements persist throughout life but do not get worse. The movements are more slow and writhing than those of chorea, but occasionally the features of both conditions are to be observed, hence the term 'choreo-athetosis'. Similar but slower movements of the proximal parts of the limbs and of the trunk are termed torsion dystonia.

Treatment. There is no specific treatment, but pallidotomy and thalamotomy may be of value, particularly for dystonia. Physiotherapy may be helpful in promoting muscular relaxation.

Kernicterus

Kernicterus is a disorder of the basal ganglia and auditory nuclei occurring in association with neonatal jaundice, particularly in premature infants. It may be caused by icterus gravis neonatorum due to rhesus group incompatibilit between the erythrocytes of mother and child (p. 738), but any severe neonata jaundice may be followed by this complication, and prematurity is mor important than Rh incompatibility.

Premature babies have a functional immaturity of the glucuronyl transferas enzyme system of the liver, and as a result of this the indirect-reacting bilirubi formed by haemolysis of any sort is not conjugated to form the direct-reacting type (p. 532). When the infant is born it is deprived of its placental excretion route, and indirect-reacting bilirubin rapidly accumulates in its blood to toxic levels which depress oxidative metabolism of brain cells, and in particular those of the basal ganglia. The danger decreases rapidly about 10 days after the birth in normal full-term infants when the liver enzyme system matures, but the premature baby is in danger for a longer period.

Clinical Features. Convulsions, coma, opisthotonos and rigidity may be early symptoms but athetoid movements or spastic paralysis, deafness of nuclear type, and mental deficiency may not be apparent until the baby is several months old.

Prevention and Treatment. Prevention depends on the early detection of haemolytic jaundice, especially in the premature child, and its prompt treatment by exchange transfusion (p. 739). Since treatment of infants with haemorrhagic disease of the newborn with large doses of some vitamin K substitutes may cause haemolysis and so increase the risk of kernicterus, only natural vitamin K_1 should be used for this disease (p. 765). There is no treatment for the established disorder and the future management is that of the child with cerebral palsy.

Spasmodic Torticollis

This is a condition characterised by involuntary movements affecting many cervical muscles on both sides of the neck. It may occur as the sole manifestation of disease of the extrapyramidal system, or it may be associated with other signs. Torticollis may also occur as a manifestation of hysteria or as a tic. The onset is usually insidious except in hysterical cases when it is often sudden following emotional disturbance. The movements consist of spasmodic rotation, flexion and extension of the cervical spine in the antero-posterior and lateral planes.

Diagnosis. Congenital torticollis due to fibrosis following haematoma of one sternomastoid muscle is present from birth. Local disease of the cervical spine, muscles or lymph glands may also cause torticollis.

Treatment. Spasmodic torticollis is a particularly intractable condition. Physiotherapy and sedation are employed but the results are usually disappointing. Surgical division of the spinal accessory nerves or of the cervical nerves may be tried if the disability is intolerable.

Tic

(HABIT SPASM)

Elaborate patterns of movement involving coordinated activity of groups of muscles occur at irregular intervals, particularly during emotional stress. The whole pattern of movements is repetitive, unlike the movements of chorea or athetosis. A tic often develops as a neurotic manifestation. It is sometimes a hysterical perpetuation of a movement which has psychological significance to the patient, or one which is involved in his work if this is of a repetitive nature.

Treatment. Early cases may respond to sedation but psychotherapy is usually necessary. It is not always effective.

CONGENITAL AND DEGENERATIVE DISORDERS

In many disorders of unknown cause, there is clinical and pathological evidence of damage which is confined to a special type of neurone, e.g. motor neurone disease. Although no causative factors have been identified, it seems probable that many of the following disorders will ultimately be classified together as being due to 'biochemical lesions'. The metabolic functions of the neurone are controlled by its cell body but when any gradual failure of any of these processes occurs the effect is first seen at the end of its axon, so that there occurs a progressive 'dying back' of the neurone from its termination towards the cell-body, associated with loss of nucleoprotein in the cell (chromatolysis). This will be seen to be the typical feature of the pathology of the 'congenital and degenerative' disorders which follow.

Case 7-4-76

Motor Neurone Disease

(PROGRESSIVE MUSCULAR ATROPHY, AMYOTROPHIC LATERAL SCLEROSIS, PROGRESSIVE BULBAR PALSY)

The cause of this disease is unknown but in occasional cases it may be familial. It is characterised by degeneration of motor neurones only, namely the anterior horn cells of the spinal cord, the motor nuclei of the cranial nerves and the corticospinal tracts.

Clinical Features. The disease begins insidiously, usually appearing between the ages of 50 and 70. The first neurones affected may be in the spinal cord or the brain stem and may be either upper or lower motor neurones predominantly. These differences of distribution have led to the recognition of three main clinical groups.

1. PROGRESSIVE MUSCULAR ATROPHY. In this form lower motor neurone damage in the spinal cord is predominant. Upper motor neurone damage may develop later in the course of the disease.

2. AMYOTROPHIC LATERAL SCLEROSIS. Both upper and lower motor neurones are affected causing a mixed picture of spasticity with progressive muscular atrophy.

3. PROGRESSIVE BULBAR PALSY. Here the brunt of the damage falls on the motor nuclei of the medulla and pons. As in the spinal types the atrophic paralysis may be associated with upper motor neurone signs in the limbs.

Though in the early stages the clinical picture may fit into one of these categories, later developments make distinctions superfluous. With the spinal types the early symptoms are weakness and wasting of the affected muscles, usually the small muscles of one hand, followed soon after by the other hand. Weakness gradually spreads proximally and is followed in a few weeks or months by similar weakness in the legs. Painful cramps may be the first symptom and very occasionally the patient may be aware of muscular twitching. Less often the atrophic weakness starts in the shoulder muscles. Sooner or later the bulbar muscles are also involved, the tongue being first affected.

On examination there is marked wasting of the weak muscles and this may cause a claw-hand deformity. The muscles to which the disease is extending (usually further up the limbs) show prominent fasciculation at rest. This becomes less evident as these muscles waste in their turn. The reflexes of the wasted muscles become depressed and eventually lost. If there is marked upper motor neurone damage the plantar reflexes are extensor and the tendon reflexes are exaggerated until the lower motor neurones forming their efferent path are destroyed by the advancing disease. Thus the peripheral wasted muscles show no reflex activity while the proximal fasciculating muscles may be spastic in amyotrophic lateral sclerosis. In the lower limbs the upper motor neurone signs are usually most evident and in some cases the patient's first awareness of the disease may be that he notices stiffness and dragging of the lower limbs, especially when he is tired.

In the bulbar types speech is severely disturbed (dysarthria) and swallowing becomes increasingly difficult (dysphagia). The muscles of the lower part of the face may be involved but the extra-ocular muscles are never paralysed. These features are usually due to the lower motor neurone lesions of progressive bulbar palsy, the signs of which are best seen in the tongue. This first shows fasciculation and fibrillation then progressive atrophy with loss of power. The palate droops, and a pool of saliva may be observed in the pharynx as reflex and voluntary swallowing are impaired. In a late stage bilateral lower motor neurone facial paralysis and paralysis of respiration occur.

Rarely upper motor neurone damage may be dominant and this causes the clinical syndrome of *pseudo-bulbar palsy*, more commonly produced by cerebral atherosclerosis causing bilateral damage to the pyramidal tracts at a high level.

In pseudo-bulbar palsy the tongue is contracted and spastic but not wasted and uncontrollable laughing and crying occur. The jaw-jerk is increased and the plantar reflexes are extensor. As with the spinal forms, both bulbar and pseudo-bulbar palsy may be associated in the one patient.

There is no sensory loss in any member of the group comprising motor neurone disease and the CSF is normal.

Diagnosis

SPINAL TYPES. Differentiation is most commonly required from the other causes of wasting of the small muscles of the hand. *Syringomyelia* does not cause such severe wasting, fasciculation is rare and there is sensory loss of dissociated type. A *spinal tumour* may cause wasting of the small muscles of the hand, but sensory loss and pain are early features and examination of the CSF may reveal a block or a rise in the protein content. *Diabetes mellitus*, *lead poisoning* and *carcinomatous neuropathy* occasionally cause a similar cord lesion. *Cervical spondylosis* involving nerve roots usually causes considerable pain, and motor and sensory loss follow a root distribution. The sensory loss extends to all forms of sensation. Signs of an upper motor neurone lesion may be found in the lower limbs when the spinal cord is involved. *Cervical rib* gives rise to pain and sensory loss, and the distribution of the wasting is usually confined to muscles innervated by the first thoracic segment. *Acute brachial neuritis* may be difficult to distinguish from the proximal type of progressive muscular atrophy but pain is greater, fasciculation is less marked, and it is not progressive. A *peripheral nerve lesion* can be distinguished by the fact that the wasting and weakness are confined to the distribution of the nerve, for example the thenar eminence in the carpal tunnel syndrome. *Arthritis* of the hands gives rise to secondary muscular atrophy but the joint involvement is obvious. *Syphilitic amyotrophy*, though rare, is important as it is amenable to therapy. Pain is usually a prominent symptom and the CSF shows the changes of meningovascular syphilis.

In all of these disorders confusion may arise because of the presence of muscular wasting. Fasciculation is absent or confined to the weak muscles. Fasciculation in powerful muscles, particularly in the lower limbs in association with wasting of the upper limb muscles, is very suggestive of motor neurone disease. A common diagnostic problem is presented by 'benign fasciculation' in which the patient is aware of coarse twitching of muscles. There is no paresis or atrophy and the prognosis is excellent. This condition occurs as a result of debility from illness or overwork. It is usually transient but may be perpetuated by psychological mechanisms. The persistent type is common in doctors and medical students who are alarmed about the possibility of motor neurone disease. In the latter condition the patient is rarely aware of the fasciculation and wasting will always be present by the time fasciculation is noticeable.

BULBAR TYPES. The two conditions most likely to be mistaken for motor neurone disease are atherosclerotic pseudo-bulbar palsy and myasthenia gravis. Pseudo-bulbar palsy is more commonly caused by arterial disease, and in these circumstances evidence of such disease is usually readily observable and often there is a history that the symptoms came on suddenly following a stroke. Severe myasthenia gravis may occasionally be confused with progressive bulbar palsy, but the absence of fasciculation, the history of variability of the symptoms in the early stages of the condition and the response to neostigmine, all make the diagnosis clear.

Treatment. There is no specific treatment, symptomatic measures being applied as required.

Prognosis. Most cases of motor neurone disease die in two to five years but there is a rare chronic type with a course of 10 to 15 years. Generalised fasciculation and involvement of the brain stem are bad prognostic signs, usually indicating death within a year.

The Hereditary Ataxias

This is a group of related hereditary or familial disorders in which the systems of neurones which 'die back' (p. 881) are mainly the spinal and brain stem tracts leading to the cerebellum, the corticospinal tracts, and the optic nerves. Different combinations of these elements form recognisable clinical pictures, which usually 'breed true' in a family, but it may be impossible to differentiate the different types during life. The group forms a link with hereditary disorders of the peripheral nerves such as peroneal muscular atrophy (p. 901) and with neurofibromatosis (p. 886) and these may occur in association with the hereditary ataxias either in one individual or in the same family. Congenital deformities, particularly pes cavus, are also commonly present.

Clinical Features. The onset may be any time from infancy to middle life. Symptoms are slowly progressive. Where cerebellar or spinocerebellar neurones are involved there is progressive ataxia of gait, followed by intention tremor of the arms, dysarthria of explosive type and, in some types, nystagmus. Where the main lesion is in corticospinal tracts there is a hereditary spastic paraplegia. Optic atrophy and loss of bladder reflexes may occur.

Friedreich's ataxia is the most common type, usually familial but occasionally sporadic. Unaffected members of the family as well as the patients may show pes cavus. There is degeneration of the spinocerebellar and corticospinal tracts, and of the posterior columns. There is therefore very severe ataxia. Tendon jerks are lost at an early stage, the ankle jerks first, then the knee jerks but finally all tendon jerks may be absent. Muscle tone is decreased. The plantar reflexes are extensor. Muscle-joint and vibration senses are impaired as the posterior column degeneration progresses. Scoliosis and pes cavus are almost invariable and other congenital abnormalities such as spina bifida and conduction defects in the heart, giving rise to ECG abnormalities, are common.

Diagnosis. The familial history, the presence of pes cavus, and the absence of remissions distinguish these diseases from disseminated sclerosis. In Friedreich's ataxia tendon reflexes are absent and there may be electrocardiographic changes.

Onset of cerebellar degeneration in later life is often due to carcinomatous neuropathy (p. 897).

Treatment. There is no specific treatment. Coordination exercises and occupational therapy will help the patient to overcome his disability in the early stages but a wheel-chair life becomes inevitable. Scoliosis and pes cavus may require appropriate appliances or orthopaedic surgery.

Prognosis. All diseases of this group are progressive but compatible with a long life.

Syringomyelia

Cavities, filled with fluid and surrounded by glial tissue, lying near to the centre of the spinal cord, are the characteristic pathological lesions in syringomyelia.

Aetiology. Central cavities were thought to result from incomplete fusion of the cord or from the inclusion of abnormal cells within the cord. These explanations may account for some cases, but it seems likely that many cavities represent dilatation of the central canal of the cord. This dilatation often results from increased pressure in the canal associated with congenital malformations of the brain in the region of the foramen magnum. Herniation of parts of the cerebellum through the foramen magnum (Arnold-Chiari syndrome) and cysts in this area are found.

The most important aetiological factor is failure of development of the foramina of Magendie and Luschka. Cerebrospinal fluid cannot escape into the subarachnoid space from the fourth ventricle since its roof is imperforate. Pressure rises within the closed ventricular system and is communicated to the central canal of the cord which expands along irregular paths of least resistance. The expanding cavity usually disrupts second order spinothalamic neurones (p. 801), often interrupts the lateral columns and may extend laterally to damage anterior horn cells. Clinical signs predictably reflect the interruption of function of these neural structures which is usually maximal in the lower cervical region.

Clinical Features. Symptoms are of insidious onset, and slow progression. Patients usually present in the third or fourth decade but signs may be detectable much earlier.

Sensory Features. Most characteristic is 'dissociated' sensory loss, i.e. loss or depression of pain and temperature sensation with preservation of the modalities of touch, vibration and position. The patient often recognises this sensory loss and seeks advice because of it. Less commonly, when pain fibres are irritated, pain in the arms is a presenting feature.

Trophic Lesions. Loss of protective sensory functions leads to painless burns and ulcers on the hands and sometimes painless, disorganised joints (*Charcot's joints*) in the upper limbs.

Motor Features. Wasting of the small muscles of one or other hand is often manifest early. Characteristically there are pyramidal tract signs in the legs.

Reflex Changes. Loss of one or more reflexes in the arms is almost invariable. Hyperreflexia in the legs and extensor plantar responses are common.

Associated Skeletal Abnormalities. Kyphoscoliosis, pes cavus and spina bifida are commonly found.

Syringobulbia. Upward extension of the cavities to involve the lower brain stem leads to dissociated sensory loss on the face, palatal palsy, Horner's syndrome and nystagmus.

Diagnosis. The conditions which may be confused with syringomyelia are discussed on page 888.

Investigations should be aimed at defining potentially treatable anomalies around the foramen magnum. Straight radiographs of this area may show bony malformations. Myelography or pneumoencephalography should be performed in order to demonstrate cysts or Arnold-Chiari malformations.

Treatment. Where causative congenital lesions are demonstrated early, surgical treatment is indicated. A variety of procedures have been used. Decompression of the foramen magnum; opening the roof of the fourth ventricle; aspiration of the cavity in the cord and occlusion, by muscle, of the upper end of the central canal, may prevent progression of the disease.

If surgical treatment is not feasible, management is directed toward preventing the patient injuring himself, and relieving pain, when present, by radiotherapy aimed at the cavity.

Prognosis. If untreated the condition is slowly progressive, and worsens if the brain stem is involved.

Neurofibromatosis

(VON RECKLINGHAUSEN'S DISEASE)

This is an autosomal dominant disorder (p. 7) in which tumours are derived from the neurilemmal sheath of the peripheral nerves, nerve roots or cranial nerves. Cutaneous fibromas, which are pedunculated tumours named mollusca fibrosa, are considered to be of similar origin. Tumours such as gliomas, meningiomas and phaeochromocytomas (p. 671) may also be associated with neurofibromatosis.

Clinical Features. A patient may show only one or many of a wide range of cutaneous or of peripheral or central neurological abnormalities. Some of the more common are *café-au-lait* patches of skin pigmentation, cutaneous fibromas and benign tumours of peripheral nerves which are discrete, movable lumps arranged along lines of nerves. The nerve trunks may be thickened or there may be a diffuse plexiform growth. Solitary neurofibromas may occur on a spinal nerve root or in a cranial nerve, especially the eighth. The tumours may also occur within body cavities, in the eyes and within the bones where they cause cystic change or kyphoscoliosis. New tumours gradually appear throughout life but the progress is slow. Any tumour may become malignant (sarcoma) but the chances of it doing so are small.

Diagnosis. Biopsy of a tumour is rarely necessary. With intracranial and intraspinal types the protein level of the CSF is very high, often exceeding 1,000 mg/100 ml. Radiology may show that an internal auditory meatus or intervertebral foramen is widened if it contains a neurofibroma.

Treatment. No treatment is required unless there is cerebral or spinal compression, or sarcomatous change, when operative removal of the tumour is necessary.

COMPRESSION OF THE SPINAL CORD OR NERVE ROOTS

Aetiology and Pathology. The more important causes of spinal cord compression are:

1. In the vertebral column: crush fracture of a vertebral body; posterior protrusion of an intervertebral disc; secondary carcinoma (from breast, prostate, bronchus or other primary sites); myelomatosis and tuberculous disease of the spine.
2. In relation to the spinal meninges: epidural abscess; tumours (meningioma, neurofibroma; infiltration with lymphomatous and leukaemic deposits; arachnoiditis and syphilitic leptomeningitis (common causes in some tropical countries).
3. In the spinal cord: tumours (gliomas, ependymoma and metastatic deposits).

Tumours, posterior disc protrusions and trauma account for the majority of cases of spinal cord compression. It is convenient in practice to divide the tumours into those arising outside the spinal cord (extramedullary), which constitute about 80 per cent, and those arising within (intramedullary).

A space-occupying lesion within the spinal canal may involve nerve tissue directly by pressure, or indirectly by interfering with the blood supply. Oedema from venous obstruction impairs the function of the neurones. Ischaemia from arterial obstruction leads to necrosis of the spinal cord. The earlier stages are reversible but severely damaged neurones do not recover so it is most important to diagnose and treat spinal compression without delay.

Clinical Features. The onset of symptoms of spinal cord compression is usually slow but it may be acute with trauma or metastases, especially if there is arterial occlusion. Pain localised over the spine or in a root distribution is the most common initial symptom. It may be aggravated by spinal movement or by coughing, sneezing or straining at the toilet which cause temporary increase in the pressure of the spinal fluid. Paraesthesiae and numbness or cold sensations may also develop early, especially in the lower limbs. Motor symptoms, which usually appear later, consist of heaviness, stiffness or weakness of a limb. Urgency or hesitancy of micturition, leading eventually to urinary retention is usually a late manifestation.

The signs found on examination vary according to the structures involved. There may be a local kyphosis if there is spinal disease, and local tenderness may be present with vertebral disease or extradural abscess. A bruit may be heard with a stethoscope over the site of a vascular tumour (angioma). Involvement of the posterior roots gives rise to hyperaesthesia and later to sensory loss over the appropriate dermatome. When the anterior roots are affected there are signs of a lower motor neurone lesion at the corresponding level. Interruption of ascending fibres in the spinal cord causes sensory loss below the level of the lesion which may be of superficial sensation or of proprioceptive sense, according to which tracts are mainly involved. Light touch, however, is often affected early. Interruption of descending fibres gives rise to upper motor neurone signs below the level of the lesion and control of the sphincters may be lost. If damage is confined to one side of the cord the *syndrome of Brown-Séquard* results. On the side of the lesion there is a band of hyperaesthesia with below it loss of proprioceptive sense and upper motor neurone signs. On the other side there is loss of spinothalamic sensation (pain, warmth and cold) as fibres of that tract decussate soon after entering the cord.

The distribution of these signs varies with the level of the lesion. Lesions above the fifth cervical segment give signs of an upper motor neurone lesion and sensory loss in upper and lower limbs (tetraplegia); a lesion between the fifth cervical and first thoracic segments gives signs of a lower motor neurone lesion and segmental sensory loss in the upper limbs and signs of an upper motor neurone lesion in the lower limbs; a lesion in the thoracic cord causes a spastic paraplegia with sensory loss having a horizontal upper level on the trunk; a lesion in the lumbosacral cord gives signs of a lower motor neurone lesion in the appropriate segments of the lower limbs and sensory loss. Spinal lesions lower than the first lumbar vertebra cannot damage the spinal cord but may damage the roots of the cauda equina.

Examination of the CSF is of great value but withdrawal of fluid may alter the pressure balance above and below the lesion in the cord and lead to rapid exacerbation of compression. For this reason, if lumbar puncture confirms the diagnosis, the patient should be referred without any delay to a neurosurgeon and if the diagnosis is highly probable on clinical grounds the puncture should be postponed until it is convenient to operate on the patient. Queckenstedt's test may reveal the features of a partial or complete block but a normal result does not exclude the diagnosis (p. 852). The cell content is normal but there is a great excess of protein (500-3,000 mg per 100 ml) and xanthochromia is present (*Froin's syndrome*). Radiological examination of the spine may reveal abnormalities at the site of the lesion but often contrast radiography, after introduction of air or a radio-opaque substance such as Myodil into the spinal canal (myelography), is required.

Diagnosis. Pain, which is so often a presenting symptom of spinal cord compression, may be wrongly attributed to such conditions as pleurisy, cholecystitis or 'rheumatism', but a careful examination will reveal signs of organic nervous disease. It is insufficient to be content with eliciting the tendon reflexes, as motor signs may be delayed long after sensory signs are present. If there is indisputable evidence of spinal cord damage it is essential to decide the site of the primary lesion. A general examination may reveal evidence of disease elsewhere making it likely that the lesion in the cord is secondary to this. A careful search should be made for a primary tumour in another organ, enlargement of lymph nodes, the cutaneous signs of neurofibromatosis and the presence of sepsis which could lead to extradural abscess. (An abscess should always be considered if pain is severe and signs of cord disease develop rapidly as immediate treatment is imperative.) If the lesion causing compression arose nitially in the spinal cord it is necessary to distinguish it from conditions such s disseminated sclerosis, syringomyelia, motor neurone disease and subacute ombined degeneration. Disseminated sclerosis appearing for the first time in middle-aged people may present as a slowly progressive lesion of the spinal ord. The differentiation from spinal cord compression is, however, so difficult nd of such importance that there should be no hesitation in seeking expert dvice.

Treatment. Surgical relief of the compression is a matter of great urgency since recovery from severe paralysis is unlikely. A delay of even a few hours may be critical in extradural abscess. Exploration is also often required to ascertain the pathological nature of the lesion. If a benign extramedullary tumour is found, it may be removed. In malignant tumours, leukaemic infiltration, and in most intramedullary lesions decompression helps little if at all. Radiotherapy may halt the course of the disease and may be of help in the relief of pain.

Prognosis. Prognosis depends on the severity and duration of the compression before it is relieved. In addition, the nature of the cause must be taken into account. Thus decompression for a malignant lesion may be undertaken though it will be of only temporary benefit.

Paraplegia

Paraplegia may result from many causes, particularly tumours, trauma and other forms of spinal compression, disseminated sclerosis, subacute combined degeneration of the cord and, in India, lathyrism (p. 169).

Treatment. This must be directed to the cause but management of the paraplegia itself is most important if complications which may in themselves lead to death are to be avoided. Pressure sores, urinary infections, renal calculi, faecal impaction and contractures are complications which can be prevented. Attention must, therefore, be given to the skin, the bladder, the bowel, the paralysed parts and to the rehabilitation of the patient.

SKIN. The skin is very liable to be damaged with the formation of pressure sores because of the loss of sensation, diminished blood supply and the immobility of the patient. The patient must be nursed on a specially made rubber mattress and the skin kept dry and clean. Every two to four hours he should be turned and nursed in such a position as will avoid pressure on bony prominences such as the sacrum and heels. This is most easily done by nursing the patient in a Stryker frame. If a pressure sore forms, the patient must not lie on the affected side and scrupulous asepsis must be observed until healing takes place. Skin grafting may be required. Nutrition must be maintained by a well-balanced diet containing adequate amounts of protein, vitamin C and iron. Blood transfusions may be required in individual cases.

BLADDER. If retention occurs, aseptic intermittent catheterisation must be carried out. An indwelling catheter may then be inserted and attached to a water-seal drainage bottle. It should be clipped and allowed to drain at regul intervals to establish reflex emptying of the bladder. As the rhythm becom established the catheter is withdrawn and the patient trained to micturate reflex at fixed times. Emptying of the bladder should be assisted by manual compressi of the lower abdomen by patient or nurse. It is not advisable to give antibioti prophylactically but if infection develops it must be treated promptly. A adequate consumption of fluid should be ensured. Frequent turning and earl ambulation where possible are the best measures for reducing the dangers urinary stagnation and calculus formation.

BOWEL. Constipation must be prevented by suitable diet and laxatives. If occurs it must be relieved by enemata; otherwise the faeces will become har and impacted and may require to be removed manually.

PARALYSED PARTS. Spasticity readily leads to the development of flexor spas and contractures in the limbs. This danger can be reduced by regular passiv movement of the limbs and by nursing the patient in such positions as wil discourage flexion of the joints. The weight of the bedclothes should be take from the lower limbs by a cradle to reduce reflex stimulation and prevent drop- foot deformity. If there is no hope of recovery, flexor spasms may be abolished by intrathecal injection of phenol in glycerine or by section of anterior nerve roots.

REHABILITATION. When the cause of paraplegia is not progressive, a great deal can be done by rehabilitation. The patient may learn to walk with calipers or to use a wheel-chair. He may thus be able to care for himself and may even follow a suitable occupation.

Cervical Disc Herniation and Cervical Spondylosis

Degenerative changes occur in the cervical intervertebral discs in the same manner as in the lumbar region (p. 892) and may lead to herniation. The herniation may affect one disc only, most commonly that between the sixth and seventh cervical vertebrae, or there may be involvement of several discs with secondary osteoarthritic changes. The latter changes (cervical spondylosis) are especially liable to interfere with the blood supply to the spinal cord, and thus lead to further damage. Osteoarthrosis in any part of the spine is a common degenerative disorder which often causes no symptoms. The clinical syndromes of acute cervical disc protrusion and chronic cervical spondylosis may occur at different times in the same patient, depending on the anatomical relation of disc protrusions and osteophytic outgrowths to the nerve roots and spinal cord, and on secondary postural or traumatic factors. Acute herniation is usually laterally situated and causes compression of a nerve root. The chronic degeneration of discs is associated with mid-line herniation and so spinal cord compression may result.

Acute Protrusion of a Cervical Intervertebral Disc. This may occur at any age, usually without apparent trauma to the neck. The patient complains of tacks of pain in the neck often termed 'cricks'. In severe attacks pain is ferred to the skin segmental area of one of the lower cervical nerve roots and o the muscles, bones and joints which it supplies. Hyperaesthesia and hyperlgesia may be found in the affected segment but sensory loss sometimes occurs. Depression of tendon reflexes utilising the affected root is common and lower motor neurone paresis of root distribution is also an occasional finding. The neck is held stiffly, and pain is produced by its movement. The spinal cord is not involved by acute herniation of an intervertebral disc in the cervical region, since this usually occurs in a dorso-lateral direction.

Cervical Spondylosis. This term is usually reserved for the disorder resulting from chronic cervical disc degeneration. The highest incidence is in the decade 60 to 70. The symptoms are of two types depending on whether the protrusion is lateral or dorso-medial.

(1) Lateral herniation of discs, with secondary calcification and osteophytes encroaching on the intervertebral foramina, causes radicular symptoms like those of the acute disc syndrome just described, but the onset may be subacute or insidious and involvement of more than one root on one or both sides is common.

(2) Dorso-medial herniation of discs which become calcified results in transverse bars which cause pressure on the spinal cord and on the anterior spinal artery which supplies the anterior two-thirds of the cord. The onset is insidious. Upper motor neurone weakness involves one or more limbs and the legs may be spastic before the upper limbs are involved. Sensory loss is most common in the upper limbs where it has a dermatome pattern but involvement of the spinothalamic tracts may cause disturbance of pain and temperature sensation in the lower limbs, and in some cases muscle-joint sense is also defective.

Pain and limitation of movement of the neck are not marked features unless a particular posture causes nipping of a nerve root.

Diagnosis. The acute disc herniation syndrome must be differentiated from other causes of brachial neuralgia (p. 900). If the eighth cervical and first thoracic roots are affected by spondylosis the pain may resemble that of coronary artery disease. Myelopathy due to cervical spondylosis may resemble tumour of the spinal cord, syringomyelia, disseminated sclerosis, motor neurone disease or subacute combined degeneration of the cord. It must be remembered that osteoarthritic changes in the spine are common and may accompany any of these diseases. For this reason it may be necessary to confirm the diagnosis by myelography. Radiological examination shows narrowing of the disc spaces and osteophyte formation with loss of the normal cervical lordosis. Oblique views show encroachment by osteophytes on the intervertebral foramina. Queckenstedt's test (p. 852) should be performed while the neck is flexed and extended, as a complete or partial block may be present when the head is in one or other of these positions. The fluid is normal unless its circulation is obstructed, when the protein may be raised.

Treatment. The acute syndrome is treated by rest in bed or by intermittent neck traction followed by immobilisation of the neck in a light metal or plastic collar. Some form of immobilisation should be maintained for at least thr months. It is important to watch for progressive cervical cord compressi but decompressive surgery is rarely required.

Prognosis. The course of the chronic syndrome is variable. After initi deterioration most cases become stationary, or symptoms and signs may resolv

The Lumbago-Sciatica Syndrome

Lumbago is pain in the lower part of the back; sciatica is pain in the distr bution of the sciatic nerve. They are not, therefore, disease entities but sympton and they are often associated.

Aetiology and Pathology. The most common cause is herniation of an inte vertebral disc. Other causes are much rarer but important to recognise. The include spinal tumour (neurofibroma and meningioma), ankylosing spondy litis (p. 779), malignant disease in the pelvis, and tuberculosis of the vertebra bodies or of the sacro-iliac joint. Degenerative changes in the intervertebra discs may appear as early as 20 years of age, but herniation is often precipitate by trauma such as twisting the spine, lifting heavy weights while the spine i flexed or during childbirth. The nucleus pulposus may bulge or rupture th annulus fibrosus, giving rise to lumbago by pressure on nerve endings in th spinal ligaments and by producing changes in the joints of the vertebral arches and to sciatica by causing congestion of, or pressure on, the nerve roots.

Clinical Features. The onset may be sudden or gradual, and may follow closely upon trauma to the back. Attacks of lumbago may precede sciatica by months or years. Lumbago is characterised by sudden severe low back pain when the patient is bending, preventing him from straightening. The sciatic pain is felt in the buttock and radiates down the posterior aspect of the thigh and calf to the outer border of the foot. It is exacerbated by coughing or sneezing which raises the pressure in the spinal subarachnoid space. Paraesthesia and later numbness may be felt over the distribution of the involved nerve root, most often the first sacral. In severe cases, weakness of the calf muscle or foot-drop may occur, according to which roots are involved. The signs associated with prolapse of an intervertebral disc may be divided into two groups.

SIGNS DUE TO ALTERED MECHANICS OF THE LUMBAR SPINE. Spasm of the sacrospinalis muscles causes flattening of the lumbar curve and scoliosis at the level of the prolapsed disc. Scoliosis increases as pain is felt if the patient tries to touch his toes. He is usually unable to do so as movement of the spine is limited. Tenderness may be found when pressure is applied to the side of the vertebral spines in the region of the affected disc.

SIGNS DUE TO PRESSURE ON THE NERVE ROOT. These depend on the particular root involved. Involvement of the first sacral root causes loss of the ankle jerk, weakness of eversion and plantar flexion of the foot, and sensory loss over the outer border of the foot (Fig. 96). The glutei may be wasted on the affected side.

nvolvement of the fifth lumbar root causes weakness of dorsiflexion of the es and sometimes foot-drop. Sensory loss occurs on the dorsum of the foot nd the lateral aspect of the leg over the fifth lumbar dermatome. The ankle rk is not affected. Involvement of the fourth lumbar root causes weakness f inversion of the foot and of the quadriceps muscle and loss of the knee jerk. ensory loss is over the medial aspect of the leg. A valuable sign of root pressure is limitation of flexion of the thigh on the affected side if the leg is kept straight at the knee (Lasègue's sign). The protein content of the CSF may be raised to about 100 mg per 100 ml.

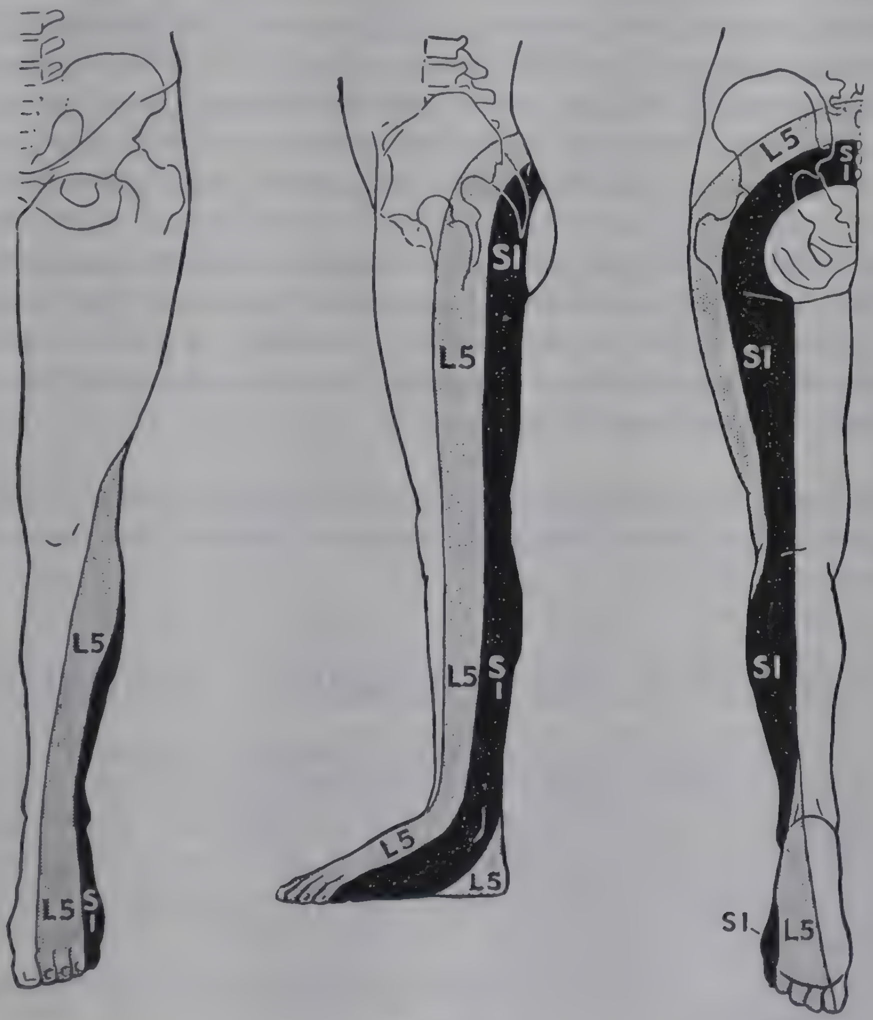


FIG. 96

AREAS OF SENSORY IMPAIRMENT IN LESIONS INVOLVING FIFTH LUMBAR AND FIRST SACRAL NERVE ROOTS

Diagnosis. The diagnosis is based on the mode of onset of the pain, its aggravation by flexion of the spine, and its relief by immobilisation, as well as on the distribution of the pain and signs of nerve root involvement. Other causes of sciatic pain can be excluded by pelvic examination and by radiological examination of the lumbosacral spine. There may be no apparent radiological change in acute disc herniation, or there may be narrowing of the disc space with osteophyte formation at the margins of the vertebral bodies. Myelography is required only if the diagnosis is in doubt or for purposes of localisati before operation. Intraspinal neoplasm as the cause of the sciatica should suspected if the CSF protein exceeds 100 mg/100 ml.

Treatment. The initial treatment in all cases is rest in bed on a firm mattr supported by fracture boards. Rest must be absolute with prohibition of t sitting position. Compromise in this respect and permission to leave bed f toilet purposes are the usual reasons for failure of this treatment. The roo most commonly involved are the first sacral and the fifth lumbar, in whi case the patient should be kept supine and no rotation of the spine permitte but in disc protrusion involving the fourth lumbar root the lateral position wi flexion of the hips is best suited to relax tension on the affected root and hen to relieve pain. Bed rest is continued for two to four weeks, after which gradu mobilisation with back-strengthening exercises is carried out over a furth period of 10 to 14 days. For middle-aged or elderly patients with chronic residu backache and a tendency to acute attacks of lumbago, a spinal support may b of great value. Cases which do not respond to rest, or in which there have bee several recurrences, may require surgery.

Prognosis. Pain usually subsides with three to four weeks of adequate be rest, but in some instances the pain becomes chronic. Recurrences are no uncommon.

NUTRITIONAL NEUROLOGICAL SYNDROMES

As with the hereditary and degenerative diseases, deficiency diseases affec particular types of cells according to their peculiarities of metabolism. The cel bodies are damaged but the neurones tend to 'die back' from the periphery The most susceptible neurones appear to be those of the peripheral nerves, the longest fibres usually being the first affected as in the polyneuropathies of beriberi, alcoholism and pregnancy (p. 167).

The spinal cord is involved in vitamin B_{12} neuropathy and the mid-brain in Wernicke's encephalopathy.

Vitamin B_{12} Neuropathy

(Subacute Combined Degeneration of the Cord)

This disease is characterised by peripheral neuropathy together with progressive degeneration of the posterior and lateral columns of the spinal cord. It is associated with Addisonian pernicious anaemia. As a result of earlier diagnosis and the introduction of highly potent remedies it is seen much more rarely than 30 years ago.

Aetiology. The disease is due to deficiency of vitamin B_{12}. It most commonly appears about the age of 50 in patients who are already known to be suffering from pernicious anaemia. Usually the treatment of the pernicious anaemia has been inadequate, though occasionally neuropathy may develop in the presence f an anaemia which is only slight. The condition may be produced by the dministration of folic acid to patients with Addisonian pernicious anaemia. Vitamin B_{12} neuropathy is rarely found after gastrectomy or other causes of malabsorption of vitamin B_{12} (p. 490).

Pathology. Degenerative changes develop in the peripheral nerves. Areas of demyelination appear in the lower cervical and upper thoracic regions of the spinal cord, particularly in the posterior columns, the corticospinal tracts and the spino-cerebellar tracts. These tracts then demyelinate and subsequently the axis cylinders break down starting from the termination of the tract and spreading towards the appropriate cells of origin. Areas of degeneration may also appear in the cerebral white matter and in the optic nerves.

Clinical Features. The disease usually develops gradually and almost invariably the presenting symptoms are due to peripheral neuropathy, usually tingling paraesthesiae of the toes, spreading later to the fingers. The patient also complains that the extremities feel cold and numb, and he may notice difficulty in holding small objects. Motor symptoms, such as weakness and ataxia, appear later but become severe as the cord is involved.

The physical signs depend on the relative involvement of the peripheral nerves and the posterior and lateral columns. Objective sensory changes are almost invariably present and consist of impairment of all forms of sensation in the distal parts of the limbs ascending in a 'stocking and glove' fashion. Sensory loss may spread on to the trunk where it may show a horizontal upper border. Tenderness of the muscles, especially of the calves, is commonly found in the early stages of the disease and indicates the presence of peripheral neuropathy. Muscle-joint sense may be impaired by peripheral neuropathy or by posterior column degeneration and either lesion may cause loss of vibration sensation. In the majority of cases ataxia is the outstanding feature. It is of the sensory type with Romberg's sign (p. 805). In the minority of cases, signs of an upper motor neurone lesion (spasticity, increased tendon reflexes and extensor plantar responses), predominate in the lower limbs. The condition of the tendon reflexes depends on the extent of involvement of peripheral neurones. Most commonly the ankle jerks are lost and later the knee jerks, though increase in these reflexes may be found. Nystagmus may be present. Visual failure due to primary optic atrophy occurs on rare occasions and, in severe cases, mental impairment is not uncommon. The CSF is normal. There is usually achlorhydria though free hydrochloric acid may be found in malabsorption states leading to vitamin B_{12} neuropathy. Examination of the blood and sternal marrow shows a macrocytic anaemia with megaloblastic blood formation (p. 728). The level of vitamin B_{12} in the serum is low (under 80 pg/ml), and its uptake from the gastrointestinal tract is impaired.

Diagnosis. The presentation of a patient with symmetrical paraesthesiae in the limbs should always raise the suspicion of vitamin B_{12} neuropathy and evidence of involvement of the posterior and lateral columns of the cord should be sought. The association with glossitis, megaloblastic anaemia and achlorhydria strongly suggests the diagnosis which should be confirmed by estimation of the serum vitamin B_{12} level. Peripheral neuropathy from other causes m present in the same way but without signs of spinal cord involvement. Tab dorsalis may be confused with vitamin B_{12} neuropathy because of the senso loss in the distal parts of the limb, absent reflexes and ataxia, but the muscl are less tender than normal, and other signs of syphilitic infection such as t Argyll Robertson pupil and changes in the CSF are commonly found. Di seminated sclerosis and myelopathy due to cervical spondylosis may give ri to damage to the posterolateral columns of the spinal cord but there are n signs of peripheral neuritis. Combined spinal cord and peripheral nerve lesio may be caused by carcinomatous neuropathy (p. 898).

Prophylaxis. The erythrocyte counts must be maintained at 5 million per cm and the haemoglobin at 14·6 g per 100 ml. It is in the patients whose anaemi is not fully corrected by appropriate treatment that subacute combined degeneration of the cord is liable to develop.

Treatment. The treatment of vitamin B_{12} neuropathy is that of perniciou anaemia (p. 730), but the dose of hydroxocyanocobalamin should be two o three times as large as is given in uncomplicated cases of pernicious anaemi and this intensive therapy must be continued as long as there is evidence o neurological improvement. Thereafter, regular maintenance doses sufficient t keep the blood normal must be given for the rest of the patient's life. Temporar increase in dosage is required if the patient develops an infection, especially if it is pyogenic, as this may lead to severe exacerbation.

Prognosis. Untreated subacute combined degeneration of the cord progresses to death within about two years. The response to treatment depends on the stage at which it is initiated. If signs are due only to peripheral neuropathy a complete recovery may be expected. Ataxia may improve remarkably. If, however, there is severe damage to the spinal cord, only limited improvement in signs such as spasticity can be anticipated although the progress of the disease can be arrested.

Wernicke's Encephalopathy

This condition is due to thiamin deficiency (p. 153), and the main pathological lesions are foci of congestion and petechial haemorrhage in the upper part of the mid-brain, the hypothalamus, and the walls of the third ventricle. The corpora mammillaria are always involved and this is believed to account for defects of memory. Vomiting and nystagmus are early symptoms but the patient most commonly presents as an acute psychiatric problem with disorientation, faulty memory, confabulation (p. 941), delusions and abnormal behaviour. This group of mental symptoms is often called Korsakoff's psychosis. Confusion may progress to stupor or coma. The predominant signs are the loss of pupillary reflexes and of extra-ocular movements. Other signs of deficiency of the B-group vitamins such as polyneuropathy may be present. The possibility of Wernicke's encephalopathy should always be borne in mind in the presence of any acute psychosis, especially when this develops in a patient who is an lcoholic, has chronic gastrointestinal disease or has been restricting his diet everely. It may also complicate hyperemesis gravidarum.

Treatment. Dramatic therapeutic responses have been obtained in early cases y the parenteral administration of thiamin. Thiamin hydrochloride (vitamin B$_1$) should be given immediately by slow intravenous injection in a dose of 50 mg and, thereafter, 50 mg should be given daily by intramuscular injection for several days. Subsequently oral administration will suffice. Thereafter a well balanced mixed diet and a natural supplement of the entire vitamin B complex such as yeast extract should be given.

Other Nutritional Neuropathies

These are described on page 167.

NEUROLOGICAL COMPLICATIONS OF CARCINOMA

Cerebral invasion or spinal compression may be the presenting feature of a metastasis from an unsuspected primary neoplasm or may augment the disability already caused by tumours arising elsewhere in the body, particularly in bronchus and breast. More than half of all cerebral tumours are secondary deposits and this high incidence emphasises the need for a careful search for a primary neoplasm in those patients who present with a picture of an intracranial space-occupying lesion.

Neurological complications may arise at a distance from a primary carcinoma in the absence of metastases.

Aetiology. The relationship between the underlying malignant process and the neurological manifestations remains obscure in most instances. Neural disturbances may occur at any stage during the development of the primary lesion and frequently antedate the symptoms directly attributable to the carcinoma by weeks or months and occasionally by as much as two or three years. At the time of neurological presentation the primary carcinoma often cannot be defined even by radiological techniques. Nor does the course of the neurological complication consistently parallel the development of the carcinoma. Immunological mechanisms, conditioned nutritional deficiencies and the direct effects of toxins produced by tumours have all been adduced as explanations of attendant neurological dysfunction but there is little supporting evidence for any of these hypotheses. Investigations have suggested the possibility that tumours may produce an alteration in protein metabolism which in turn interferes with the synthesis of enzymes and hence cause neural dysfunction. It is likely that progressive multi-focal leucoencephalopathy p. 898 results from virus infection in patients whose immunological responses have been impaired by chronic disease.

The neurological features evoked by distant carcinoma are protean: they may affect singly, or in combination, muscles, peripheral nerves as well as central neural structures and the brain. The syndromes presented are mc conveniently categorised anatomically.

Myopathy, Myositis and Myasthenia. A proximal weakness of late onsc usually first affecting the legs may be due to a lesion of muscles secondary to distant carcinoma. Histologically the muscle may show changes of a non-specif myopathy or there may be collections of inflammatory cells, characteristic c polymyositis. Sometimes the myopathic weakness is markedly exacerbated b exertion producing a myasthenic syndrome. Weakness and fatiguability usuall most often affect the legs, and less commonly the arms; bulbar and ocula affections are uncommon in contrast to myasthenia gravis. Fatiguability of muscl may sometimes be improved by an intravenous injection of edrophoniur hydrochloride but this response is inconstant and is often poorly sustainec The electromyographic picture in these carcinomatous myasthenic syndrome differs from that produced by myasthenia gravis. Guanidine 40-50 mg kg bod weight sometimes improves muscle power in carcinomatous myopathy.

Peripheral Neuropathy. Peripheral neuropathy is probably the commonest o the distant neurological complications of carcinoma. Clinically the neuropathy is usually of mixed sensory-motor type (p. 901). The cerebrospinal fluid protein content is often raised to more than 100 mg per 100 ml. Much less commonly a pure sensory neuropathy may be manifest, almost always in association with a bronchial carcinoma of oat-cell type. Pathological lesions in this rare condition are mainly situated in the dorsal root ganglia where there is degeneration of the sensory neurones.

Spinal Cord Affection. Carcinomata may produce a picture which resembles motor neurone disease with loss of anterior horn cells, accompanied sometimes by upper motor neurone signs. Uncommonly this picture, which mimics amyotrophic lateral sclerosis, may be accompanied by a bulbar palsy. Necrosis affecting the cells and the tracts of the spinal cord, maximal in the thoracic segments, is a rare complication of carcinoma.

Subacute Degeneration of the Cortical Layers of the Cerebellum. This is an uncommon manifestation of distant carcinoma. Ataxia, affecting upper and lower limbs, is a consistent presenting feature; dysarthria too is often found but nystagmus is present in only a minority of cases.

Encephalopathy. This has occasionally been found in patients suffering from carcinoma particularly of the bronchus, breast and uterus. The most common presentation is an insidious and progressive dementia with memory disorder and sometimes mood disturbance. These psychiatric and mental symptoms may occasionally be accompanied by features of brain stem involvement such as double vision or bulbar palsy and often there are accompanying pyramidal tract signs.

PROGRESSIVE MULTI-FOCAL LEUCOENCEPHALOPATHY. This rare disease does not seem to occur as an independent state but occurs late in the course of an ntecedent disease, e.g. reticulosis or carcinoma. The pathological findings com-rise widely disseminated demyelinating lesions in the brain together with istinctive changes in the glial cells suggestive of invasion by one of the papova roup of viruses. It is a condition of rapid and progressive nature usually leading o death within a few weeks or months of its being manifest. The clinical icture varies widely. Hemiparesis is the commonest disability but dysphasia, ysarthria, and hemianopia are also frequent. Dementia may occur, as may onvulsions.

Treatment. The treatment of the neurological complications is that of the primary lesion. Improvement, and occasionally complete remission, of a myasthenic-myopathic syndrome may occur with removal of the primary tumour but this is by no means invariable. Carcinomatous motor neurone disease often tends to halt its progress despite the fact that the primary carcinoma continues to grow. Clearly the treatment for the underlying malignancies is imperative but the response of the neurological complications is unpredictable.

DISORDERS OF PERIPHERAL NERVES

A rational approach to disorders of peripheral nerves should be based on the recognition of their fundamental structure. The cells of origin lie in the anterior horns of the spinal cord and the dorsal root ganglia. Axons represent elongated processes of these cells. They are enveloped by a series of Schwann cells, forming the fatty myelin sheath. Pathological processes which primarily affect cell bodies may first manifest themselves at the distal ends of axonal processes.

Many diseases affect peripheral nerves whose pathological reactions may, however, be grouped under two broad headings:

(1) *Parenchymal neuropathy* where the lesion affects (*a*) nerve cells or their axons, or (*b*) the myelin sheath.

(2) *Interstitial neuropathy* where the pathological process primarily affects the connective tissue or blood vessels of nerves.

Although these rather stereotyped pathological reactions do not lead to distinctive clinical features, a knowledge of the pathological nature of a neuropathy is particularly helpful in assessing its course and prognosis. The clinical classification of peripheral nerve lesions is best based on their anatomical distribution.

Mononeuropathy

This term refers to affection of a single nerve. Trauma is a common cause. Sustained pressure or stretching of nerve occurs in a variety of situations. The radial nerve is commonly implicated as, for instance, in the 'Saturday night' palsy which results from bizarre sleeping postures caused by drunkenness. The ulnar nerve at the elbow and the common peroneal nerve at the head of the fibula are also frequently involved. The signs are those of lower motor neurone paresis and sensory loss in the distribution of the respective nerves. Complete recovery of function in four to six weeks is almost invariable.

Nerves may also be compressed whenever they pass through or near rigid anatomical structures, particularly fibro-osseous tunnels. This type of lesion, called an *entrapment neuropathy*, is one of the most frequent affections of peripheral nerves. *Compression of the median nerve in the carpal tunnel* is the commonest entrapment syndrome. It occurs most frequently in middle-aged women and is then usually unaccompanied by other disease. It may also be a complication of pregnancy, myxoedema, acromegaly or rheumatoid arthritis. The patient complains of pain, numbness, tingling or an 'electric shock' feeling in thumb and fingers supplied by the median nerve, especially after using the hand or in bed at night when it may waken the patient from sleep. There is sometimes objective sensory loss of the radial three and a half digits and there may be weakness and wasting of abductor pollicis brevis and opponens pollicis muscles. The condition is often bilateral. Rest and splinting at night should be tried. Local injection of hydrocortisone is sometimes effective if there is no muscular wasting. Thyroxine therapy relieves the carpal tunnel syndrome in myxoedema. The syndrome occurring in pregnancy usually disappears in the puerperium but may be relieved by the use of diuretics. If these measures are unsuccessful the condition can be rapidly relieved by surgical decompression of the nerve in the carpal tunnel.

The lower trunk of the brachial plexus may be compressed at the thoracic outlet, especially if there is a *cervical rib*. Nocturnal pain in the arm and sensorimotor disturbance in the C_2-T_1 distribution are relieved by rest and physiotherapy. Operative treatment is rarely necessary.

The lateral cutaneous nerve of the thigh is frequently entrapped at the inguinal ligament giving rise to paraesthesiae and pain over the anterolateral aspect of the thigh (*meralgia paraesthetica*).

Mononeuritis Multiplex

In this condition several spinal nerves are damaged concurrently or serially. Clinically signs are limited to discrete neural territories. Leprosy is a common cause of this picture in some geographical areas. Polyarteritis, and other connective tissue disorders, diabetes mellitus and sarcoidosis may also give rise to multiple peripheral nerve lesions.

Localised Radiculopathy

Demyelination of a localised group of nerve roots may give rise to the disorder called *neuralgic amyotrophy* or *acute brachial neuritis*. This condition sometimes follows a vaccination or inoculation and an immunological mechanism may be responsible. It may also occur after infection, injuries or operations.

The patient complains of severe pain over one shoulder girdle, sometimes spreading up the neck or down the arm. Simultaneously, or two or three days later, paralysis develops in the painful muscles. These are usually supplied by the fifth and sixth and less commonly the seventh cervical roots so that the deltoid, spinati, and serratus anterior muscles are usually involved, and frequently also the muscles of the upper arm. The tendon jerks disappear in the affected limb and wasting is rapid. Sensory loss is slight or absent. If present it is usually on the outer aspect of the upper third of the affected arm. The brachial plexus is often tender.

Sometimes paralysis of single nerves of the upper limb occurs and occasionally both shoulder girdles are involved. Constitutional symptoms are mild or absent. The CSF is normal or shows only slight lymphocytosis (10-15 per cmm).

Pain usually subsides in one to two weeks. Recovery from paralysis is slow. It usually takes several months, but eventual complete recovery after two or more years is usual. Recurrent attacks of neuritis in the same or the opposite shoulder rarely occur.

Corticosteroids should be tried in neuritis believed to be the consequence of an allergic mechanism. Otherwise treatment is symptomatic and along the lines of those adopted for poliomyelitis.

Generalised Polyneuropathies

In this group of conditions discrete neural affection is not manifest. There is a generalised affection of all nerves. The most common clinical picture is a symmetrical dysfunction of both motor and sensory nerves first manifest at the distal part of limbs.

Aetiology. There are many causes of this clinical syndrome. Some of the more important are:

Hereditary. Peroneal muscular atrophy; hypertrophic interstitial neuropathy.

Metabolic. Diabetes mellitus and porphyria.

Deficiency. Vitamin B_{12} neuropathy (p. 168), beriberi (p. 153), alcoholism and gastrointestinal disease.

Poisons. Lead, arsenic, mercury, triorthocresylphosphate (ginger paralysis). In addition many new substances produced for therapeutic and industrial purposes carry this hazard.

Infectious and Toxic or Allergic Reactions. Leprosy is an infection of peripheral nerves. Diphtheria causes toxic neuropathy. Polyneuropathy associated with exanthematous disease and inoculations is probably allergic in nature. Acute infective polyneuritis, for long believed to be due to a virus, may have a similar cause.

Connective Tissue and Vascular Disorders. Polyarteritis (p. 305) and disorders such as systemic lupus erythematosus cause mononeuritis multiplex.

Malignant Disease. Carcinoma of the bronchus and other tumours may cause polyneuropathy which may be the first manifestation of malignancy.

Pathology. The peripheral nerves show Wallerian degeneration or segmental demyelination. In acute cases little may be found at autopsy since the early changes are biochemical in nature.

Clinical Features. Polyneuropathy presents with paraesthesiae such as tingling, pins and needles and numbness in the periphery of all four limbs, usually starting in the toes and in addition there may be great pain. These symptoms gradually spread proximally as shorter fibres are involved so that the distribution does not follow that of any particular nerve root or peripheral nerve. The patient then has difficulty with fine movements such as fastening buttons because of developing loss of proprioception or he notices that objects feel 'different'. Sensory ataxia may follow and weakness soon becomes apparent. Weakness, too, usually starts peripherally and spreads proximally.

Examination reveals impairment or loss of all forms of sensation, extending from the periphery of the limbs in a 'glove and stocking' fashion. A characteristic feature is that the muscles are often extremely tender to pressure. Damage to the motor fibres causes the signs of a lower motor neurone lesion, especially at the periphery of the limbs, so that wrist-drop and foot-drop may appear. The proximal muscles are later involved and then the trunk and sometimes the face. Respiration may be endangered by paralysis of the intercostal muscles or the diaphragm. Interruption of the reflex arcs causes loss of the tendon reflexes.

There are features peculiar to certain forms of polyneuropathy.

ALCOHOLIC POLYNEUROPATHY. Pain is usually severe and other evidence of alcoholism may be apparent, such as tremor of the hands, mental impairment or signs of liver disease.

LEAD NEUROPATHY. Lead poisoning causes paralysis of muscles, usually within the distribution of the radial or lateral popliteal nerves, but without involving all muscles supplied by these nerves. It is, for instance, common to find paralysis of the extensor muscles of the wrists and fingers with sparing of the brachioradialis and abductor pollicis longus muscles. Some authorities consider that this is due to local poisoning of muscles rather than true neuropathy. There is no loss of sensation. Other clinical features associated with chronic exposure to lead are anaemia with punctate basophilia of red cells (p. 719) and a blue line on the gums if the patient is not edentulous. If the amount of lead ingested is sufficient to cause poisoning there may be colic and headache and acute or chronic encephalopathy, causing mental changes and epileptic seizures. The clinical picture may resemble that of porphyria.

PORPHYRINURIC POLYNEUROPATHY. This form of neuropathy is often purely motor in type. It is associated with temporary mental disorder and attacks of abdominal pain. The urine contains porphobilinogen (p. 588).

DIABETIC POLYNEUROPATHY. This is discussed on page 706.

DIPHTHERITIC POLYNEURITIS. This is discussed on page 66.

ACUTE 'INFECTIVE' POLYNEURITIS. (Guillain-Barré syndrome.) This condition begins with headache, vomiting, pyrexia and pain in the back and limbs. It is caused by inflammation with oedema of the spinal nerves soon after their formation by junction of the nerve roots. After a variable period of hours or days paralysis appears, beginning usually in all four limbs simultaneously, though sometimes starting in the lower limbs and spreading in ascending fashion. Unlike other types of polyneuropathy, proximal rather than distal muscles in the limbs may be affected. The trunk and respiratory muscles may be involved and also the muscles supplied by the cranial nerves, particularly the seventh. Sensory loss may be confined to the limbs or may spread on to the trunk. Reflexes are lost and sphincter difficulties occur. Death may be caused by respiratory or bulbar paralysis (p. 882). The CSF shows striking changes, there being a normal cell count but a great increase in protein (100-1,000 mg per 100 ml). If death from respiratory paralysis is prevented or avoided, the outlook is good, as most cases recover in three to six months. The evidence for an infective aetiology is unsatisfactory. The possibility of an autoimmune mechanism provides a rationale for the use of corticosteroids.

POLYARTERITIS (p. 305). This causes multiple mononeuritis rather than symmetrical polyneuritis. Motor and sensory loss will be distributed according to the nerves involved rather than according to length of fibre so the 'glove and stocking' distribution is absent.

Diagnosis. Pain in the limbs occurs from causes such as ischaemia or arthritis and will be unaccompanied by abnormal neurological signs. Tabes dorsalis causes lightning pains, absence of the tendon reflexes and sensory loss. The description of the pain however is different, there is decreased rather than increased muscle tenderness and Argyll Robertson pupils are usually present. Acute infective polyneuritis is often mistakenly diagnosed as poliomyelitis but in the latter disease the weakness is asymmetrical, there is no sensory loss and the CSF changes are different (p. 867). Motor neurone disease should not be confused as no sensory loss occurs in that condition. Nevertheless motor neurone disease and polymyositis (p. 908) may be difficult to differentiate from motor forms of polyneuropathy. If lower motor neurone and sensory signs are restricted to the lower limbs the possibility of a lesion of the cauda equina should be considered.

Treatment. Prevention is very important. Any new drug which is liable to cause neuropathy must be used with care and industrial hazards should be avoided by protective clothing, exhaust ventilation and other techniques advised by the industrial medical officer. When polyneuropathy has developed as a result of exposure to a toxic substance the first step is to remove the patient from further exposure. When the cause is nutritional or metabolic the appropriate treatment must be initiated without delay. Thus therapy may be required for beriberi, diabetes or pernicious anaemia. Corticosteroids are indicated for acute 'infective' polyneuritis. Chelating agents, sodium calciumedetate or D-penicillamine are used in the treatment of lead poisoning.

In severe cases bed rest is essential since the nervous control of the heart may be defective and cardiomyopathy is sometimes associated. The limbs should be supported in the optimum position, and passive movements carried out several times a day. A cage should protect the feet from the weight of the bedclothes. Respiratory insufficiency may require tracheostomy or institution of intermittent positive pressure respiration (p. 332). When recovery begins, active movements should be carried out under the supervision of a physiotherapist.

Myasthenia Gravis

This condition is characterised by undue fatiguability of certain muscle groups, with incapacity to sustain muscular activity.

Aetiology. The cause of the disease is unknown but is in some way related to a disorder of the thymus gland. There is strong evidence for a breakdown of immune tolerance (p. 37). A thymoma is present in 15 per cent of cases and the gland contains an excess of germinal centres in the remainder. Myasthenia is sometimes associated with thyrotoxicosis, Hashimoto's disease, rheumatoid arthritis or pernicious anaemia. There are slight histological changes in the muscle fibres and motor nerve terminals, but the typical fatiguability is considered to be due to a failure of transmission at the myoneural junction. The nature of this disorder, which produces an effect resembling curarisation, is unknown.

Clinical Features. The disease usually appears between the ages of 15 and 50 and females are more often affected than males. It tends to run a remitting course. Relapses may be precipitated by emotional disturbance, infections, pregnancy and by severe muscular effort. The cardinal symptom is abnormal fatiguability of muscles so that a muscular movement, though initially strong, rapidly tires. Intensification of symptoms towards the end of the day or following vigorous exercise is characteristic. The first symptoms are usually intermittent ptosis or diplopia but weakness of chewing, swallowing, speaking or of moving the limbs also occurs. Any muscle of a limb may be affected, most commonly the shoulder girdle muscles, so that the patient is unable to undertake work above the level of the shoulder, such as combing the hair, without frequent rests. Respiratory muscles may be involved and respiratory failure is a not uncommon cause of death. Asphyxia occurs readily as the cough may be too weak to clear foreign bodies from the airways. The symptoms fluctuate in intensity, long periods of remission being common during the early years. Muscle atrophy may occur in long-standing cases. There are no signs of involvement of the central nervous system.

The remarkable therapeutic response to an intramuscular injection of neostigmine (1·5 mg) is a valuable diagnostic aid. Edrophonium has a similar action and is invaluable for test purposes as the response is almost immediate, while any unpleasant parasympathomimetic effects are very brief. An initial dose of 2 mg of edrophonium is injected intravenously and a further 8 mg half a minute later if no undesirable reactions (fasciculation, sweating, colic) occur. This test also helps in the diagnosis of 'cholinergic crisis' since weakness due to overdose of anticholinesterase drugs is increased, but only for a few minutes. It should be noted that some muscle groups may be overdosed while others still require more neostigmine. It is, therefore, important to observe the status of the muscles of respiration and swallowing rather than those of the eyes.

Diagnosis. Most myasthenic patients are at first considered to be suffering from *hysteria* because the absence of physical signs when the patient is examined after a rest seems incompatible with the description of severe weakness and because attacks are often precipitated by emotional disturbances. *Disseminated sclerosis* may be suggested by the intermittent nature of the symptoms and the frequent occurrence of diplopia and dysarthria. The bulbar type of *motor neurone disease* may also be confused at first, but weakness does not disappear with rest or with edrophonium. *Polymyositis* (p. 908) and *carcinomatous myopathy* (p. 898) may closely resemble myasthenia gravis because at the onset of these conditions there is often a phase of muscular weakness which responds to neostigmine. *Muscular dystrophy* is progressive and, in the more common types, the extra-ocular muscles are not involved.

Treatment. The sheet anchor of medical treatment is neostigmine, but this must be given in adequate dosage (15-45 mg orally every two to four hours). In severe cases neostigmine may require to be given subcutaneously in doses of 1-3 mg several times daily. Fifteen minutes before neostigmine is injected, atropine sulphate, 0·6 mg should be injected subcutaneously to diminish the undesirable side-effects of neostigmine such as bowel colic. Pyridostigmine gives less prompt relief than neostigmine but has a more prolonged action with fewer side-effects. Hence it gives relief during the sleeping period and is also of value for those patients unable to tolerate adequate amounts of neostigmine. The 60 mg tablet of pyridostigmine is equipotent with 15 mg of neostigmine. In some resistant cases it may be necessary to give very large doses of anticholinesterase drugs. This should be done only in hospital as overdosage causes another type of neuromuscular block ('cholinergic'), especially when long-acting preparations which tend to be cumulative are used. Early evidence of a cholinergic crisis is the presence of fasciculation, pallor, sweating, small pupils and excessive salivation. Atropine should be given at once and preparations made to sustain respiration artificially if required. Specific antidotes (oximes) are of little practical value.

The general management of the patient's life is important in order to reduce fatigue and stress. In the severe case the early signs of respiratory embarrassment should be detected so that artificial respiration can be started in time. Spontaneous remission sometimes occurs, but it is rarely of long duration. Thymectomy offers the best prospect of permanent cure or great amelioration of myasthenia. The most suitable cases are young women with myasthenia of less than six years' duration. Older women and men are less often helped, but thymectomy should certainly be considered for all patients who do not respond satisfactorily to drug treatment. If there is radiological evidence of a thymoma it is customary to irradiate it before removing the gland. Operation is usually unnecessary in a benign type of myasthenia in which the weakness remains confined to the extra-ocular muscles.

Prognosis. The prognosis is very uncertain, particularly in the presence of a thymoma, when it tends to be worse than with simple thymic hyperplasia.

DISEASES OF MUSCLE

Myopathies

Diseases of muscle are not diseases of the nervous system, but as some of thei manifestations may be readily confused with neurological conditions som relevant examples are described here. There are obvious exceptions, but it is useful generalisation that muscular disease affects mainly the proximal muscle of the limbs whereas neuropathic disease (polyneuropathy or motor neuron disease) affects mainly the distal muscles.

Myopathy is a generic term subsuming all primary diseases of muscle. It ma be subdivided into:

1. Genetically determined myopathy—(*a*) progressive muscular dystrophy and (*b*) myotonic dystrophy.
2. Congenital myopathies.
3. Metabolic myopathies.
4. Inflammatory myopathies or myosites.

1. Genetically Determined Myopathy

(a) Progressive Muscular Dystrophy

This is a group of hereditary disorders characterised by progressive degeneration of groups of muscles without involvement of the nervous system. The wasting and weakness are symmetrical, there is no fasciculation, tendon reflexes are preserved until a late stage and there is no sensory loss. Several clinical types have been described, but from a prognostic viewpoint three major groups can be distinguished.

1. PSEUDO-HYPERTROPHIC TYPE (Duchenne type). This is transmitted by a sex-linked recessive gene occurring almost exclusively in males. The disease usually appears within the first three years of life, beginning in the pelvic girdle and lower limbs and later spreading to the shoulder girdle. About 80 per cent of cases show an initial pseudo-hypertrophy involving the calf muscles, quadriceps, glutei, deltoids and infraspinati. Contractures are common. The affected muscles are larger and firmer than normal, but are nevertheless weak. The weakness gives rise to a characteristic waddling gait, and when rising from the supine position, the child rolls on to his face and then uses his arms to push himself up. Death occurs from inanition or respiratory infection by the middle of the second decade.

2. LIMB GIRDLE TYPE (Juvenile scapulo-humeral type of Erb). The gene carrying this disorder is inherited as an autosomal recessive, affecting both sexes. It usually appears in the second or third decade. It starts in either the shoulder or pelvic girdle and later spreads to involve both. The rate of progression is variable; it may be slow, with long periods of arrest, but severe disablement usually occurs within 20 years and the patient does not survive to middle age.

3. FACIO-SCAPULO-HUMERAL TYPE (Landouzy-Déjerine). This type is inherited by an autosomal dominant gene so that several siblings of both sexes may be

ffected. It appears at any age, first in the facial muscles and then in the shoulder irdle. After many years the pelvic girdle may also be involved. The disease rogresses very slowly with periods of arrest and is compatible with a long life.

Diagnosis. Hereditary muscular dystrophy must be distinguished from (*a*) ongenital myopathies; (*b*) acquired myopathies in which treatment is possible r spontaneous remission may occur; (*c*) from myasthenia gravis; and from *d*) diseases of the lower motor neurone. Acquired myopathies occur alone 'polymyositis', p. 908) or as part of dermatomyositis, endocrine disease or arcinomatous myopathy (p. 898). Spontaneous recovery may occur or there may be improvement with steroid therapy. Myasthenia gravis shows exacerbations of weakness with effort, and responds to injection of edrophonium or neostigmine.

Diseases of the lower motor neurone from which muscular dystrophy must be distinguished are (*a*) motor neurone disease which is associated with fasciculation, (*b*) peripheral neuropathy in which there is distal involvement of muscles and sensory loss, and (*c*) residual poliomyelitis which is commonly mistaken for muscular dystrophy, if the history of the acute illness is not known, but the lesions are asymmetrical and not progressive.

The diagnosis of muscular dystrophy is readily confirmed by electromyography (EMG) or muscle biopsy. Aldolase, or creatine kinase and other enzymes which are usually intracellular, are increased in the serum, especially in the rapidly advancing Duchenne type. Serum enzyme changes may be found before other clinical signs enabling early detection of the disease in siblings. Less severe changes of the same type are found in women who carry the abnormal gene of the Duchenne type.

Treatment. No effective treatment is known. Deterioration may occur with excessive confinement to bed. Physiotherapeutic and orthopaedic measures may be required to counteract deformities and contractures.

(b) Myotonic Dystrophy

Myotonia consists of slow relaxation of muscles due to hyperexcitability of the muscle cell membrane. *Mytonia congenita* (Thomsen's disease) is inherited as a Mendelian dominant and appears in early childhood. The only symptom is the slow relaxation of a muscle if it is contracted voluntarily or by mechanical stimulation. The patient may be unable to relax his grasp or to open his eyes if they have been closed tightly. The muscles may be unusually powerful in early life.

Dystrophia myotonica (myotonia atrophica) is also hereditary and appears between the ages of 20 and 30. There is wasting of the facial and temporal muscles, sternomastoids, shoulder girdle, forearms, quadriceps and leg muscles, and all these and the tongue show myotonia after voluntary contraction or after percussion of the muscle. Ptosis is prominent. Unlike most muscular diseases, distal muscles are more severely affected than proximal. There is also cataract, frontal baldness and gonadal atrophy leading to impotence and sterility in men and amenorrhoea in women.

Treatment. There is no treatment for the muscular dystrophy, but if myoton is troublesome it can be relieved by procainamide, 0·5-1·0 g q.i.d., quinin sulphate 300-600 mg t.i.d., or diphenylhydantoin 100 mg t.i.d.

2. Congenital Myopathies

This group of rare myopathies presents in infancy with muscular weaknes and limpness. Serum enzymes tend to be normal or slightly raised. The EM is usually myopathic. The mode of inheritance is variable. They are name according to the type of structural abnormality found in the skeletal muscl fibres. Most cases are non-progressive or only slowly progressive.

3. Metabolic Myopathies

Many conditions are associated with muscle disease. Among the more important are:

Thyrotoxic Myopathy. Mild weakness of the proximal muscles of the limbs is a common feature of thyrotoxicosis. In a few patients muscular wasting and weakness predominate, and the other manifestations of hyperthyroidism may not be obvious.

Corticosteroid Myopathy. Weakness of the pelvic girdle may occur in Cushing's syndrome and as a result of treatment with corticosteroid hormones.

Familial Periodic Paralysis. This is characterised by attacks of profound weakness, lasting for several hours and often occurring after exertion or after a heavy carbohydrate meal. In the common variety the attacks of weakness are accompanied by a fall in the serum potassium level (p. 190).

4. Polymyositis

This group of muscle diseases is characterised by damage to muscle fibres accompanied by the interstitial infiltration of inflammatory cells. Clinically, muscle weakness and wasting may be patchy and may be accompanied by muscular pain and tenderness. Dermatomyositis is described on page 781. Often the diagnosis can be made with certainty only be a muscle biopsy. When a myositic picture presents in middle age it may be associated with occult carcinoma. Some cases of myositis respond to treatment with corticosteroids.

THE PREVENTION OF DISEASES OF THE NERVOUS SYSTEM

The preventive aspect of disease of the nervous system is largely concerned with the infective and deficiency diseases but there is increasing recognition of inherited biochemical disorders which can be influenced by dietary or other means. Kernicterus may be prevented by the prompt recognition of haemolytic disease in the newborn, followed by immediate exchange transfusion. Phenylketonuria can be recognised by a simple urine test in infancy before clinical anifestations arise, and these can be prevented by a special diet. Asymptomatic iblings of a known case of hepato-lenticular degeneration can be detected y biochemical tests and further neurological damage minimised by the use f chelating agents such as penicillamine. A major advance in the Duchenne ype of muscular dystrophy is the discovery that the female carrier can be etected by serum enzyme studies and advised of the risk of transmitting the isease to any male children which she may bear. Congenital porphyria can lso be detected by examination of the blood and urine and the hazard of olyneuropathy prevented by avoidance of barbiturates. Huntington's chorea s also a hereditary disease but eugenic measures are not possible as the signs do not appear until after the main reproductive period.

Outbreaks of meningococcal meningitis can also be controlled by the isolation of cases, the prophylactic treatment of contacts (e.g. with sulphadiazine) and the prevention of factors which favour the spread. The prevention of tuberculous meningitis involves the same factors as the prevention of tuberculosis in general. Neurosyphilis is preventable by proper treatment of primary infection and by careful follow-up of those infected, to ensure that asymptomatic neurosyphilis is not overlooked. Poliomyelitis can now be prevented almost completely by suitably repeated vaccination.

Vitamin B_{12} neuropathy can be eliminated by the early diagnosis and efficient treatment of pernicious anaemia. Peripheral neuropathy due to nutritional causes can also be avoided by ensuring an adequate diet. Early recognition and treatment of diabetes mellitus and alcoholism may prevent peripheral neuropathy. Polyneuropathy due to toxic causes may also be prevented by the careful use of therapeutic substances which are known to have a tendency to cause this condition, and also by the avoidance of industrial hazards.

The scope of preventative treatment in the vascular diseases is not great. The recognition and surgical treatment of cerebral aneurysms before rupture occurs may, however, prevent the more devastating effects associated with subarachnoid haemorrhage. The value of anticoagulants in ischaemic cerebral disease is debatable, but during periods of a few months when embolism is a hazard or the blood-flow through the carotid and vertebral arteries is undergoing adjustment, their use may prevent cerebral infarction.

In many other conditions where the primary lesion is not as yet preventable, a great deal can, nevertheless, be done to minimise its effects. Efficient treatment in the early stages of conditions such as disseminated sclerosis greatly reduces the incidence of the more distressing complications such as massive bed sores, contractures, painful flexor spasms and ascending urinary infection.

C. MAWDSLEY.
J. A. SIMPSON.

Further Reading:

Matthews, W. B. & Miller, H. (1972). *Diseases of the Nervous System*. Oxford: Blackwell.—A concise readable account of neurological disorders, intended for undergraduates.

Brain, Lord & Walton, J. N. (1969). *Diseases of the Nervous System*. 7th ed. London: O.U.P.

Elliot, F. A. (1971). *Clinical Neurology*, 2nd ed. Philadelphia: Saunders.—Both of these are authoritative and comprehensive textbooks designed for postgraduate students but very suitable reference works for undergraduates.

Jennett, W. B. (1970). *An Introduction to Neurosurgery*, 2nd ed. London: Heinemann. —A succinct and clearly written introduction to surgical neurology.

Adams, R. A. & Sidman, R. L. (1968). *Introduction to Neuropathology*. New York: McGraw-Hill.—Though it deals in considerable detail with pathological processes this book is particularly valuable because of its extensive discussion of the correlation of pathological lesions and clinical features.

Psychiatry

PSYCHOLOGICAL illness is so common that it is encountered daily in all branches of the practice of medicine. Psychological medicine is not the preserve of the psychiatrist alone; not only must the initial diagnosis be made by the general practitioner but treatment of most cases of mental ill-health is undertaken by him. Psychiatrists see only a minority of psychiatrically-ill patients. What is more, the effectiveness of modern drugs in controlling the symptoms of schizophrenia and of depression has made it possible for general practitioners to treat in the community many patients who formerly would have had to be admitted to a psychiatric ward. Another important reason for all doctors to be knowledgeable about psychiatric disorders is that organic and psychiatric disorders commonly co-exist in the same patient.

Psychiatry deals with three large groups of patients: the major disorders, the minor disorders and mental retardation.

1. The major psychiatric illnesses or psychoses interfere with a patient's perceptions, thinking and feelings so profoundly that at times what he says to his fellow-men no longer makes sense to them, and he is regarded as insane.
2. There are many patients with less gross disorders who remain in touch with their surroundings; they suffer from psychoneuroses, personality disorders, psychosomatic illnesses, sexual deviations or addictions.
3. Mental subnormality is a congenital handicap, present from birth or an early age, unlike psychiatric illnesses which supervene after a more or less normal psychological development.

Classification

A brief classification of mental disorders will help the reader to familiarise himself with their names. To start with the psychoses, these are of two types, organic or functional.

Organic Psychoses. In these organic brain syndromes the functioning of the brain is impaired either by a physical lesion (trauma, tumour or infection) or by a toxic or degenerative process. Organic brain syndromes when acute are known as *delirium*. Examples are the toxic confusional states occurring with brain trauma, cerebral anoxia, infection, or intoxication with barbiturates, amphetamines or alcohol.

The chronic psychoses, where an irreversible brain lesion has occurred, are the *dementias*. The most common are those associated with advancing years—cerebral atherosclerosis and senile psychoses. Mild degrees of dementia make the patient forgetful, easily confused, irritable and emotional; more severe dementia results in disorientation, gross loss of memory and deterioration in personal habits.

Functional Psychoses. These are the major psychiatric illnesses occurring without brain disease or impairment, which so far have eluded all attempts at explanation in terms of physical or biochemical pathology. The two most common forms are *manic-depressive psychosis*, in which the principal symptom is a profound disturbance of the patient's mood, and the *schizophrenias* in which the patient's thoughts become bizarre and strange, so that he loses contact with his fellows, and with his surroundings.

The Psychoneuroses. These represent by far the most common forms of psychiatric illness encountered in general medical practice. They are conveniently subdivided into anxiety neurosis, hysterical neurosis, obsessive-compulsive neurosis, phobic neurosis and depressive neurosis.

Personality Disorders. This term is used to describe patients whose personalities differ markedly from the normal population. Their abnormality takes the form of recurrent disturbance in relationships with other people. In addition to their social difficulties, they present traits (e.g. hostility, passivity) not found to the same degree in the behaviour of normal people. Patients with moderate degrees of personality disorder are distressed by their inability to get on constructively with others and often seek treatment; otherwise they do so when they are further disabled by psychoneurosis or psychosomatic illness. Those with gross degrees of disorder (sociopathy) interfere disruptively in the lives of their relatives and associates, and may come into conflict with the law; they may not regard themselves as abnormal, and reject any efforts to treat them.

Psychosomatic Illnesses. These are the extremely common illnesses (such as some cases of asthma, peptic ulcer, dermatitis, ulcerative colitis, etc.) which emotional factors help to precipitate or to prolong.

Sexual Deviation. People not conforming sexually to the prevailing norm most often consult (or are brought to) their doctor only when their abnormality has become seriously disturbing to their relatives or has put them into conflict with the law. Some, however, are themselves distressed by their deviation and may on occasion need psychiatric treatment for complicating psychiatric disorder, such as a depressive illness or paranoid reaction. Now that sexual relations between consenting males over 21 is no longer a crime in Britain, homosexuals are less vulnerable socially.

Drug Addiction. An addict is physically or psychologically dependent on a drug and suffers distressing side-effects when deprived of it.

Alcoholism. An alcoholic is an excessive drinker who is unable to stop drinking although to do so has become necessary because of health impairment, marital strife or difficulties at work.

Mental Subnormality. In intelligence defect present from infancy two categories are distinguished. Subnormality implies that although the intelligence level is below normal (I.Q. below 80), the child may benefit from teaching and social training. Severe subnormality refers to those so handicapped that they require very considerable attention and support, and are incapable of leading an independent existence. The most common single cause of severe subnormality is Down's syndrome (mongolism, p. 12). A definite cause of subnormality is found only in a minority of cases, and then various clinical conditions can be responsible, e.g. phenylketonuria, cretinism, etc. Patients who are mentally subnormal may also suffer from other mental illnesses. They may, for example, become depressed, or schizophrenic, but when this happens the symptoms of their mental illness will be modified by their basic handicap of mental backwardness.

Incidence of Psychiatric Morbidity

Serious psychiatric illness is relatively infrequent: about 1 in 200 of a general practitioner's adult patients is likely to suffer from severe depressive illness in the course of a year; the incidence of schizophrenia is much less, but since this illness runs a long course the cases tend to accumulate. The overall prevalence of schizophrenia, as shown by community surveys, is just under 1 per cent. As people grow older the occurrence of organic psychoses due to disease of the brain becomes increasingly common. The frequency of minor forms of psychiatric illness, such as neurosis, personality disorder and psychosomatic disorders is very much greater. Careful counts have shown that minor psychiatric illness occurs every year in no less than 14 per cent of the patients on a general practitioner's list: if one includes cases in which psychological factors significantly influence co-existing physical complaints, the count rises to over 40 per cent.

Patients with emotional disorders tend to consult their doctors more often than patients with physical diseases and complain of a wider variety of symptoms. As a result, they are often referred to a succession of clinics for specialist investigation, and commonly undergo minor or major surgery without avail. This involves a waste of both the doctors' and the patients' time, which could be avoided if the psychological disorder had been recognised and treated at an earlier stage. It is therefore necessary for every practitioner to include a psychological appraisal as part of the clinical examination of his patients. This is a skill which has tended to be neglected in the past, but now medical schools provide clerkships in psychological medicine; where this has been done, medical students have shown themselves able to acquire the necessary technical skills quite rapidly.

The Psychiatric Examination

It should be emphasised that attention should be paid to the patient's emotional state not only when a frank psychiatric illness is suspected, but in the course of every thorough clinical examination. Psychiatric disturbances can be elicited (*a*) while taking the history, and (*b*) while examining the patient's mental state.

Before discussing these two aspects of the psychiatric examination, it is necessary to draw attention to certain ways in which functional nervous illnesses differ from other illnesses. From the beginning of our clinical studies, most of us have been taught to think in terms of *disease entities*; that is, we assume that our patient is suffering from a particular disease with its specific aetiology, pathology, signs and symptoms. Our clinical examination is therefore so organised as to make sure that we do not overlook indications of pathology in any of the major bodily systems, and our history-taking consists largely of a form of cross-examining of the patient in order to elicit further clues. The whole exercise is a sort of detective-work with the aim of unmasking the disease which is causing our patient's symptoms. The disease entity model serves admirably in certain pathological conditions, notably in the case of sudden acute infections caused by identifiable micro-organisms such as acute lobar pneumonia or virus hepatitis or the exanthemata of childhood. It can be adapted, although less neatly, to chronic and degenerative conditions, but here one may have to take into account a number of contributory factors both in the host and in the environment, and also a wider range of manifestations of the disease.

Only a few psychiatric illnesses conform to the classical disease entity model. These are described above as the deliria, the acute organic psychoses; they are due to infection, toxins or direct trauma affecting the brain; instances are febrile delirium, amphetamine psychosis, acute porphyria, post-traumatic confusional state. Here, just as in an acute infection, there is one all-important aetiological factor, and effective treatment depends upon its being recognised in the course of the clinical examination.

With a few exceptions, most of the other major psychiatric illnesses (such as schizophrenia, manic-depressive psychosis and the senile psychoses) correspond to the category of chronic and degenerative diseases: that is, they are variable both in severity and in the particular pattern of symptoms which they present, and they appear to be due to multiple causal factors in which heredity usually plays a significant part.

This still leaves the minor psychiatric disorders and the psychosomatic disorders unaccounted for. Because they are usually associated with bodily discomfort, patients naturally consult their doctors about these complaints; many medical-sounding names have been coined, like anorexia nervosa or globus hystericus or cardiac neurosis, and as a result it is easy to assume that each such diagnostic term refers to a separate disease process. Here, however, the 'disease orientated' model can be misleading. In addition to their symptoms patients suffering from these conditions can also be found to have highly complex disturbances in the relations with people close to them. These maladaptive patterns of behaviour in personal relationships have been learned by life-experience; the life of the neurotic or psychosomatic patient has included some painful, frustrating or damaging experiences which still disturb his peace of mind and interfere with his performance.

When we operate with the 'disease orientated model in mind, our task is to identify the particular disease as quickly and as economically as possible; when we operate with the 'faulty learning' model in mind, our business is to elicit our patient's worries, his sensitivities, his irrational fears and the difficulties he is currently having with the people most important to him. Then we try to reconstruct the stage in his earlier emotional development where things went wrong. If the patient can be helped to recognise such setbacks in his past, the possibility presents for him to clarify how early experience continues to be expressed in his current relations with people. He may then modify his self-damaging ways of reacting to others.

The Psychiatric History

The first essential in taking a good psychiatric history is to help the patient to express what is really troubling him. When a medical student 'sits in' on his first few psychiatric interviews, he is apt to be struck by the psychiatrist's apparent inactivity. In fact, the more skilled the interviewer, the less he needs to say. He prompts the patient with an occasional, quite general remark, such as: 'Can you tell me what caused you to consult your doctor?', and then 'Tell me more about those attacks of breathlessness (or headaches, or fits of depression)'. Often an inarticulate, encouraging murmur is enough to help the patient to bring out more relevant information. Although he holds his tongue, the interviewer is far from inactive: he must convey a real interest in what the patient has to say, and above all he must let the patient feel that he will not be shocked, angry or disdainful, no matter how embarrassing or unpleasant may be the content of what is uttered. Really painful feelings are never easy to communicate. Sometimes a patient will back away from such feelings and start talking about trivialities, or try to engage the interviewer in a social conversation; as soon as this happens, one can sense a drop in the emotional tension of the interview, and it is necessary to take him back to the sensitive topic, by simply repeating some of his words: 'You said a moment ago . . .' and let him take it on again from there. Some interviewers are better than others at being alert to their patient's feelings, but everyone can heighten their sensitivity in this respect with practice. In so doing, one learns to use one's own personal response to the patient as an instrument of investigation—less accurate, no doubt, than a blood sugar estimation, but just as important in its proper context.

This open-ended interview may yield important clues within 10 or 20 minutes; by now some of the patient's current sources of anxiety, and the types of social situation in which they occur, should become apparent. It is now time for the interviewer to become more active, asking some guiding questions about the patient's father, mother and siblings, and about his relationships with these important members of his parental household. This enquiry is made because in the great majority of cases of emotional disorder the faulty learning which finds expression in symptoms dates back to painful childhood experiences.

The interviewer next asks about the patient's schooling and his occupational career. By this stage in the interview, he should have gained the patient's confidence sufficiently to be able to broach the sometimes embarrassing, but often crucially important topic of his sexual development and his intimate associations with other people. It is essential that the interviewer should be able to show that he is not shocked or disturbed by whatever the patient has to tell him. This is not easy at first, because unpractised interviewers may find themselves reacting with strong personal feelings of sympathy, disgust or anger; but it is precisely in acquiring control over one's own responses, while still maintaining a lively interest when eliciting details about the patient's personal life, that one becomes a skilled interviewer.

The interesting thing about an interview of this kind is that it often begins with a purely physical complaint, such as constipation, backache or dyspepsia; then, as the patient is able to provide more personal details, links become evident between the initial complaint and current stresses or conflicts. Dyspepsia may be provoked by difficult relations with one's boss and these in turn may recall painful relations with one's father; the investigation of a particular patient's dyspepsia may be incomplete unless these factors have been elicited and further explored. Before the end of the interview the presenting symptoms can again receive attention by careful physical examination and consideration whether a barium meal or other special investigations are required.

Psychological treatment begins the moment that the patient and doctor meet, for the latter's personality and attitude to the patient and his illness are powerful therapeutic factors which operate immediately. The first therapeutic step is the taking of the history. If this is done patiently, thoroughly and objectively the patient feels interest is being taken in his case, and that his problem is being understood. A spontaneous account of the illness by the patient should be encouraged first, further details being filled in later. Too systematic an approach to the history often results in a mass of facts being obtained, but the nature of the problem, from the patient's point of view, being entirely overlooked.

Examining the Mental State

As the interview proceeds, the interviewer will want to extend his observation of the patient's current mental functioning. It helps to do the examination of the mental state in a systematic manner, first paying attention in turn to the patient's appearance and behaviour, mood and thought processes. Thereafter attention is paid to the patient's interpretation of his environment and to his intellectual functions.

APPEARANCE AND BEHAVIOUR. Some patients talk rapidly, jumping from subject to subject, some frequently lose the thread of what they are saying and need to be prompted, while others talk slowly, in dull flat tones which may indicate depressive illness. At the same time, the patient's non-verbal behaviour should be noted, i.e. whether his attitude and gestures are tense and restless, or heavy and slow. In some cases we may be struck from the very start by something unusual about a male patient's dress or a woman's make-up. Before jumping to hasty conclusions, however, especially where young people are concerned, one has to make sure that the oddity is indeed an individual one, and not merely the latest trend of teenage fashion.

MOOD. After he has noted the information provided by the patient's appearance and behaviour, the interviewer needs to learn about the patient's mood, that is whether he feels cheerful or depressed, confident or fearful, suspicious or bewildered. In ordinary social encounters, we do this all the time, but we observe the restraint of good manners, in that if a companion does not wish to reveal his feelings, we respect his reticence, even though we may suspect that he is, as we say, only 'putting a brave face on it'. In the clinical situation, these rules do not apply: we must make it our business to find out how he is really feeling. Many patients need some help before they can unburden themselves of fears, anxieties or feelings of intense unhappiness. Some patients are ashamed to mention some emotional disturbances, such as a phobia, which is a feeling of intense anxiety experienced in certain settings, e.g. in open spaces, or on public transport, or when eating in public. Once these painful feelings are revealed, they are readily recognisable. A greater effort of attention has to be made in order to recognise the *lack* of emotional response of any kind, which is characteristic of some schizophrenics. Sometimes these patients will make our task easier by themselves complaining of their inability to experience emotions in the way they used to do; at other times one is simply aware of an inability to elicit any real warmth, any sense of human contact with the patient, and this failure of rapport should alert one to the possibility that he may be schizophrenic.

THOUGHT PROCESSES. The third task in the examination of the mental state is to observe any peculiarities in the patient's talk. In form his talk may be abnormal through hesitancy, incoherence, changes of topic, sudden silences, or bewildering shifts from one topic to another: all these disorders can be features of schizophrenia. He may speak very rapidly, with puns and rhymes, as occurs in mania. His talk may be laboured, slow and flat and indicate a depressive state.

Repetitive thoughts characterise obsessional psychoneurosis, an important feature of which is an *obsession*, a persistent idea which the patient cannot get rid of; the repetitiveness may be extremely distressing even when the patient recognises the idea as absurd, e.g. a girl may ponder whether she could be pregnant, although she knows perfectly well she has not had intercourse.

INTERPRETATION OF HIS ENVIRONMENT. The interviewer next ascertains if the patient's perceptions are accurate. He may be unduly sensitive to glances or chance remarks. He may suffer from *illusions*, misinterpretations of sensations arising from real stimuli: a patient with delirium tremens may misinterpret furniture as menacing persons. *Hallucinations* are sense perceptions, such as visions, which occur in the absence of any kind of external stimulus. *Delusions* are false beliefs, such as that one is being slowly put to death, to which the patient adheres even when demonstrably wrong; a man with a hypochondriachal delusion, e.g. a depressed patient convinced he has venereal disease, persists in his morbid notion despite medical evidence. A schizophrenic may be firmly of the belief that he has changed sex. These are signs of major illness.

INTELLECTUAL FUNCTIONS. While listening to what he tells us, we can at the same time pick up clues about the patient's intellectual level from his choice of words and from the ease or difficulty with which he expresses himself. If there is reason to suspect that he may be intellectually impaired, one can test his *general information* by posing simple questions, such as asking him to name the Prime Minister, the capitals of the larger countries in Europe, or to perform simple sums of mental arithmetic. The best clues to mental retardation, however, are given by the patient's scholastic record and by the type of job which he has been able to perform in adult life. We note whether he knows the date and time of day, and recognises where he is and to whom he is talking: this tests his *orientation* for time, place and person. Impairment of mental function is commonly shown by *inability to concentrate*, to 'take things in', and hence to remember recent events. This may become apparent during the interview or it may be elicited by asking the patient to remember a name and address or a telephone number and then asking him to repeat it after an interval of one or two minutes. The final step in the mental state examination is an assessment of the patient's degree of *insight* into his condition; that is, does he recognise that he is ill or is he wrongly convinced that it is his environment and his fellows that are at fault?

Formulation

When the history has been taken, and an examination of the mental state completed a thorough physical examination should be carried out, and following this appropriate investigations when required. Such intervention needs to be handled well. Investigations which are necessary must be carefully planned, and quickly executed, and then a halt must be called. The pernicious habit of 'just having one more test' must be avoided as it undermines the confidence of the patient in the certainty of the diagnosis; the practitioner must be able to decide how much evidence is required to elucidate the nature and the cause of the disorder, and having obtained it, he must act upon it.

The doctor is now in a position to draw up what may be described as the *formulation* of the case, which is a brief assessment of the nature of the disturbance, and the part that particular intrinsic and extrinsic factors have played in its development. A *formal diagnosis* should be made because it helps to clarify one's own thinking and also helps one to set about the next task which consists in drawing up a *plan of treatment*. This will have a somewhat different emphasis, depending upon whether the patient's illness falls in the general class of neurosis, personality disorders, functional psychosis or organic mental illness, but in each case psychiatric treatment (like all good medical treatment) should start with the attempt to understand both the disorder and the person who is suffering from it. The advent of new and powerful drugs has tempted some doctors to forget that their patients are not merely 'biological preparations' on which interesting pharmacological experiments can be carried out; they are themselves active participants in the processes of cure and recovery. This has been shown again and again, in demonstrations of the 'placebo effect', and it is particularly important in all forms of psychiatric illness, where a patient's confidence in his doctor contributes so largely to his peace of mind.

The Psychoneuroses

In describing some of the particular syndromes of psychiatric illness we shall give priority to those which are most frequently met with in general medical practice, namely the psychoneuroses and personality disorders. The former category includes the *anxiety neuroses* in which disturbance of mood is the most prominent feature, *hysterical neuroses* and the less common *obsessive-compulsive* neuroses.

Anxiety Neurosis

Anxiety may be defined as a state of anticipation of something unpleasant about to happen, accompanied by a feeling of inner tension, and somatic manifestations such as tense muscles, sweating, tremor and tachycardia.

Although anxiety is a symptom of many psychological disorders, in anxiety neurosis it dominates the picture, and other symptoms are but minor features of the total illness; this is the most common form of psychoneurosis.

Aetiology. Research has shown that hereditary factors play a part, although a relatively small part, in the genesis of anxiety neurosis, manifestations of anxiety being found a little more frequently in the patient's parents than in the population as a whole.

This is not surprising, because not only laboratory workers but also breeders of dogs and of racehorses know that nervous excitability is a recognisable genetic trait. In human subjects, however, it appears that emotionally disturbing experiences during the early formative years play an even more important aetiological role. These traumatic experiences need not be dramatic, single events; a sudden severe fright may cause a child to become timid and to have nightmares and other symptoms for weeks or months, but if he has the support of a stable, affectionate home life, he will outgrow such an isolated trauma. On the other hand, if a child's early years are attended by prolonged insecurity, for example, when one or both parents are so burdened by their own problems that they let their child feel unloved, if not unwanted, or where a brother or sister seems to receive preferential treatment, or where a mother's own exaggerated anxieties impart an excessive timidity to her child, then there may be a profound undermining of the child's self-confidence.

This may not be apparent for several years, particularly if the experiences of school life and early adolescence have been free of alarming or painful incidents: but a setback in early adult life may precipitate adult emotional illness. Painful events, such as bereavements, reverses in a love affair, disappointments in one's career, being obliged to contend with disagreeable or frankly hostile people at work, or being involved in prolonged domestic strife, may cause a vulnerable individual to succumb to feelings of anxiety, interfering materially with his ability to cope with the day-to-day routine. The adult setback will often be found to have similarities with an earlier childhood emotional trauma.

Clinical Features. The illness may take many forms: it may be an acute anxiety state, often severe in intensity, appearing against a relatively normal background, or a chronic anxiety state, present since adolescence in mild degree, but subject to periodic exacerbations according to the tide of life's fortunes.

The outstanding feature of the illness is the anxiety, with its accompanying feeling of inner tension and unpleasant anticipation. Sometimes the anxiety is fear of a potential danger but often it is a diffuse feeling unrelated to any particular dreaded event. (A *phobia* develops when the anxiety is associated with a specific form of activity such as travelling in a bus or train, and so much may this be dreaded, that the patient is eventually housebound through being unable to travel at all.) The anxiety fluctuates in intensity, being sometimes a mild feeling of tension or nervousness, but at other times a state of panic, in which the patient may be overwhelmed by a feeling of terror, which is no less disturbing because he is unable to say just what it is that makes him so afraid.

This state of anxiety gives rise to other symptoms. The ability to concentrate is impaired, and constant fears make decisions difficult. There may be a continuous state of restlessness of varying degree, or extreme irritability. Fear of insanity or of committing suicide commonly afflicts these patients though, in fact, both are extremely rare. Preoccupation with bodily functions and fear of serious illness (e.g. cancerphobia) are frequently manifested. The continued stress exhausts them so that they lack energy and perseverance, and feel that they can no longer carry on with their work.

Somatic symptoms are also prominent. There is a general tenseness of the musculature, with hyperactivity, especially of the fingers and hands, shown in such movements as screwing up a handkerchief or constantly intertwining the fingers. A fine tremor of the fingers is present, and profuse perspiration, especially of the palms and forehead, is common. The pulse rate is raised, the blood pressure labile and overactivity of plain muscle is commonly manifest by frequency of micturition or of calls to stool. Breathing is often rapid and feelings of nausea and flatulence occur; headache of tension type, dizziness and unsteadiness are frequently mentioned. The patient sleeps badly, finding it difficult to get off to sleep, and being easily disturbed. Appetite is poor, and loss of weight may be a pronounced feature. Disturbances of menstruation are common.

Diagnosis. Not uncommonly the patient omits mention of his distressing emotional state, and complains to his doctor only of the somatic accompaniments of anxiety; unnecessary special investigations can be initiated or diagnostic errors made if the doctor omits to ask about the state of the patient's mood.

The patient's hypochondriacal fears often raise the question of co-existing physical disease, and it may prove necessary to supplement a thorough physical examination with appropriate ancillary investigations. It is scarcely surprising that some patients who know that they suffer from diabetes, angina, peptic ulceration, renal failure or other forms of chronic disease undergo episodes of severe anxiety which is in part at least related to a real threat to their lives. These patients with psychological complications of organic disease have to be distinguished from those who are crippled by an unjustified fear that they have just such diseases (hypochondriasis); the differential diagnosis is prompted by a negative physical examination, but clinched only when the patient has been helped to give free expression to his fears, and in so doing permits a positive diagnosis of neurotic illness to be made.

Differentiation from other forms of psychological illness is less difficult. Though hysterical, obsessive or depressive symptoms may be present in an anxiety state, the diagnosis can usually be made on the totality of the picture, anxiety and its accompanying manifestations dominating the scene. It is rarely difficult to distinguish an acute anxiety state from a case of depressive psychosis with severe agitation and restlessness. A carefully taken history will reveal the underlying severe depression, with feelings of unworthiness, guilt and failure, and frequently delusions about impending, and merited, punishment. This form of depression is so intensely distressing to the patient that the risk of suicide is especially high, so it is particularly important to establish the diagnosis. If doubt remains, further study of the case in hospital is advisable.

Treatment. When the formulation of the case indicates that emotional factors are prominent, some form of psychotherapy is required; simply informing the patient that there is nothing wrong with him, or that he must pull himself together, is useless. Even telling the patient that his difficulties are psychological and indicating the emotional problems in his life is unlikely to be of benefit, because although he may acquiesce verbally, his emotional tension will not be thereby lessened; he needs an opportunity for exploration and clarification, and for gaining greater insight into the nature of his difficulties.

Such insight may be gained by a series of discussions, for which periods of at least half an hour or longer should be set aside, in which the patient is encouraged to talk about his difficulties. Initially, the discussions should be allowed to proceed in any direction the patient desires; subsequently, aspects of his problems which come to seem relevant may be suggested by the doctor as themes for discussion. The error that is commonly made with this form of psychotherapy is for the doctor to talk too much by lecturing the patient and giving advice. In order that the patient may achieve a better knowledge of himself, it is essential that he should do most of the talking, the doctor saying little, but maintaining an attitude of interest and expectation. If the patient's flow of talk is arrested, encouragement can often be given, without diverting him from his present theme, by repeating his last phrase in query form. Thus, if he says, 'I found the job far too much for me', and then becomes silent, after giving him ample time to resume spontaneously, the doctor may say, 'You found the job far too much for you?', which starts the patient off again. The effect of this approach is first that the patient feels better for having talked to someone about his troubles; a second effect is that frequently the patient comes to grasp more accurately the nature of his problems, and will, at that stage, often accept suggestions and interpretations which, if given earlier, would have been rejected. Often what emerges is that the patient is having difficulties with a person of importance to him: a spouse, a parent, or an employer for example, and that he needs to improve on his management of the relationship. He may be too dependent on his wife, too docile to his parent, or too subservient to his employer, in which case his interviews should encourage greater assertiveness.

When the psychological disorder takes the form of somatic symptoms, and fear of bodily disease is prominent, it is not sufficient simply to tell the patient that there is no evidence of organic pathology; he will at once suspect that he is being accused of malingering, if not of being 'mental'. It is necessary to let him know that his distress and his symptoms are recognised as genuine and in need of exploration. It is often possible to use events in the patient's own experience to illustrate the influence of emotion on bodily functions. Many people can recognise what it feels like to be sick with excitement, to be aware of a pounding of the heart in moments of fear or to experience frequency of micturition when keyed up before an examination. At a general level, however, this understanding becomes much more meaningful when, in the course of an emotionally-charged interview, the patient has been able to see for himself that his physical symptoms are clearly related to particular aspects of his own private life, recurring during the interview as he *describes* particular problems. Patients are further convinced about this when they have been helped to go one stage further, to confront the painful situation, and to master it, e.g. the patient can say to his employer that he considers he is being exploited and his abilities insufficiently recognised. When this is done, there is commonly an immediate, even if temporary, relief from the distressing symptom, together with a sense of accomplishment which encourages the patient to persevere with further efforts of self-discovery.

It is important, at the same time, not to overlook physical factors, such as anaemia or faulty nutrition, which can be rectified. A poor physical condition in itself gives rise to symptoms which further aggravate the anxiety of the patient. Should drugs be employed as an adjunct, their specific purpose should be made abundantly clear, so that no possibility will arise of the patient feeling that their prescription indicates that he is suffering from an organic disease. Measures such as these are often adequate for a mild anxiety state with somatic symptoms, when the emotional problems are not too great.

The use of drugs to obtain reduction of distressing mood disturbance is often a necessary preliminary to effective psychotherapy. A very anxious patient will not be able to concentrate sufficiently to benefit more than partially from clarification of conflicts discussed during an interview. Diazepam and chlordiazepoxide are effective anxiety-reducing drugs (p. 943). The phenothiazines, though widely used, are more likely to give rise to lethargy or drowsiness but thioridazine can be of value when the patient is both fearful and restless.

In the treatment of all forms of neurotic illness it is important to decide what can best be done, within the limitations of resources for treatment and in the circumstances of each individual patient. For example, one may recognise that a patient has shown a life-long pattern of minor phobias and proneness to worry, but that recent events in his personal life have caused one particular phobia (such as the fear of going into crowded places) seriously to interfere with his normal activities. Here, the principal aim of the treatment should be limited to helping him to master the presenting symptom. Behaviour therapy is a form of psychological deconditioning or desensitisation, often effective when a single disabling phobia, such as agoraphobia (fear of open spaces) constitutes the clinical picture. Explorative psychotherapy, which calls on the patient to take stock of his relationships with people close to him and to modify some of his habitual patterns of behaviour towards them, can also aim to relieve pressing symptoms without attempting to effect any radical change in his personality.

The same is true of many hysterical symptoms and of exacerbations of psychosomatic disorders. By focussing upon recent events in the patient's personal experience and exploring their emotional significance for him, many patients can be helped to reconstitute that *modus vivendi* between personal quirks and practical necessities which, for most of us, represents normal mental health.

Hysterical Psychoneurosis

It is important to remember that 'hysteria' is a term which is used in one sense by lay people, and in a different sense in medical parlance. In popular speech, to be hysterical means to lose control of one's feelings, and to behave in an extravagant, socially embarrassing manner. Psychiatrists, on the other hand, distinguish between *hysterical personality disorder* and *hysterical illness*. The individual with hysterical personality disorder is emotionally immature, elf-centred, attention-seeking and child-like; but we all know people who show these attributes to a certain extent but still manage to function reasonably well, even if they remain rather dependent on other people's attention and support.

Hysterical psychoneurosis consists of the reproduction of the symptoms or signs of an illness by a patient for some personal purpose without his being fully aware of his motive in doing so. Familiar examples are sudden 'blackouts' or 'loss of memory' which enable a patient to evade a particularly painful or embarrassing occurrence. The unawareness of his motive distinguishes the patient with hysterical neurosis from the malingerer who deliberately and consciously simulates illness for some purpose. The differentiation of the two can usually be made in practice as the malingerer is unable to maintain the fiction under questioning and examination.

Aetiology. Heredity is even less important in the development of hysterical neurosis than it is in anxiety neurosis, and plays but a minor role in its aetiology. Environment, by contrast, is of great moment not only in producing the hysterical type of personality, but also in providing those situational factors which precipitate the development of hysterical symptoms. Lack of emotional security in the early years can encourage, and prolong a state of childlike dependency. Such persons, denied the development of confidence to tackle practical difficulties by themselves, tend to continue to rely on infantile devices, such as denial, magical thinking and looking to others to solve their problems.

During the First World War, hysterical symptoms occurred much more frequently among 'other ranks' than among officers, who were subject to anxiety neurosis; during the Second World War, as a result of the general increase in the standard of education and sophistication, anxiety states were much commoner than hysterical symptoms in all ranks of the military forces. Frank hysterical symptoms were, however, still commonly found among members of the British Pioneer Corps, which was a repository for able-bodied but intellectually limited citizens, and also among the hardy, but simple and untutored peasants who fought in General Tito's army of Jugoslav partisans. Gross hysterical symptoms occur frequently in association with educational and intellectual retardation.

CONVERSION TYPE. This form of hysterical psychoneurosis includes the illnesses in which the patient presents with a mimic physical lesion, such as sudden blindness, or paralysis of one or more limbs, or total loss of sensation in a part of the body. Careful neurological examination will often reveal that the disability does not correspond to the anatomical areas served by motor or sensory nerves: instead, the lesion illustrates the patient's often naïve idea of what it is like to lose the power of his right hand, or to be unable to walk. In many cases, the patient has acquired a concept of a particular affliction as a result of seeing someone who was dramatically handicapped—perhaps a case of poliomyelitis, of angina, or of epilepsy. The mimicry is the result of autosuggestion, the patient becoming suddenly overwhelmed by the conviction that he is similarly afflicted. The form the symptom takes may be symbolical, a when the attitude of crucifixion is adopted in a hysterical fit, or it may be dete mined by identification with another person, as when the daughter, after h mother's death, develops the symptoms of her mother's last illness.

The grosser forms of conversion symptoms are not so common today a they were a generation ago, but instances of involuntary mimicry of physica ailments are still frequently encountered in cardiac, gastrointestinal and orthopaedic clinics, and are a particularly common complication of injuries where compensation award enters the picture. A striking feature of conversion i that although the patient may be quite severely incapacitated by his symptoms he appears remarkably unconcerned about them. This is because the incapacit has in fact intervened to remove a cause of anxiety, so that the patient feel strangely relieved, although he is not aware of the reason for his being so calm

The precipitating cause of a hysterical illness is usually an emotionall charged situation, the inexorable and unpleasant consequences of which th patient cannot face, and so he excludes it from consciousness, and escape from the situation (or makes himself the object of solicitous attention) b means of his symptoms.

DISSOCIATIVE TYPE. This form of hysterical psychoneurosis includes the numerous altered states of awareness, such as faints, fits, amnesias, trances. twilight states and forms of multiple personality. A fugue state is one in which the patient wanders away from home in a state of altered awareness. Hysterical stupor, when the patient lies motionless showing no reaction to the environment, is sometimes seen; in psuedo-dementia the patient behaves as if insane.

Clinical Features. The list of hysterical symptoms and signs is co-extensive with that of physical illness, for there is no clinical feature which may not be woven into the hysterical pattern. Some features, however, occur more commonly than others and may be arbitrarily divided into two groups, sensory and motor. Sensory symptoms may be of the special senses such as blindness and deafness, or in the somatic sphere, when cutaneous and deep sensibility in their various forms are lost. The sensory loss does not obey anatomical or physiological laws, but follows the patient's concept of the disability. Cutaneous sensory loss may have a sharp horizontal upper margin on the limb. In monocular blindness, the use of coloured letters and glasses may reveal that the patient is seeing with his 'blind' eye. There may also be positive sensory symptoms such as headache, pain, tinnitus and so on.

Motor symptoms consist of aphonia, mutism and paralysis and rigidity of movements. These again are not anatomical in distribution, and often a muscle seemingly paralysed when employed as an agonist, is found to be acting when used as a synergist or antagonist. Positive clinical features in the motor sphere consist of tremors, tics and explosive utterances, spasm of ocular muscles, abnormal gaits and fits. These fits may vary from simply falling to the grounds as in syncope, to bizarre attacks with wild movements of arms and legs. They can usually be distinguished from epileptic attacks by the absence of cyanosis or pallor, the increased violence of the movements when restraint is applied, the absence of incontinence and the preservation of reflexes such as the corneal.

Carpopedal spasm and other manifestations of tetany may result from hysterical hyperventilation.

ANOREXIA NERVOSA. In this condition patients emaciate themselves (pp. 523 and 628). Anorexia nervosa is often classified with the hysterical psychoneuroses. Frequently preoccupied about food, the patient stubbornly seeks to become extremely thin. The determination to diet is a disorder of motivation. Sometimes eating binges occur, after which the patient may induce vomiting. Exertion of the will so that over-riding priority is given to becoming thin, is the chief feature of the disorder. It often follows teasing about being plump.

Young girls are mainly affected. If questioned suitably, they often reveal preoccupations (sometimes so distorted as to reach delusional proportions) that they may be pregnant. They have other fears relating to sex, sometimes following misinformation by parents; however, these girls also give evidence of great fear at growing up and accepting mature feminine responsibilities. They are often in a hostile relationship with their mothers. Often there have been upsetting life experiences, such as separation from or death of a parent. In addition to dread of sexual development, girls with anorexia nervosa often show athletic preoccupations, and are overactive physically. Amenorrhoea at times precedes marked emaciation. The usual mood state is cheerful high spirits, but depression can occur. Patients usually reject treatment and show unconcern about their physical deterioration.

In-patient psychiatric treatment with psychotherapy to achieve emotional maturation is necessary, in addition to correction of the eating disorder.

Diagnosis. The diagnosis of hysterical psychoneurosis can be the most difficult in medicine. Three steps are required: the first is to identify the psychoneurotic syndrome on the basis of its characteristic symptomatology, as described above. Only after such positive diagnosis need steps be taken, should any doubt still exist, to demonstrate that there is no organic disease which can account for the symptoms and signs. Error in labelling a symptom due to an organic lesion as hysterical would be infrequent, however, if the diagnosis were not made until the third step was also taken: this consists of discovering what situation the patient subconsciously seeks to avoid, and showing how the development of symptoms has achieved this object. If evidence of previous hysterical breakdowns can be uncovered, the diagnosis is more secure. It should always be remembered, however, that the stress of organic disease may provoke a superadded hysterical reaction in a person so disposed. An axiom worth remembering is that alleged hysterical neurosis appearing for the first time in a stable person in middle life, has almost always an organic basis.

Treatment. The treatment of hysterical psychoneurosis may be a difficult problem; removal of a symptom can often be achieved by a prolonged session, in which intense persuasion is used, but, if the precipitating situation is unaltered, relapse is usual. The method may be justified, however, in certain circumstances as when aphonia prevents discussion, or when loss of memory prevents the patient from communicating his identity or revealing the events which precipitated his illness.

The principles described for treatment of anxiety neurosis (p. 921) are al relevant in hysterical psychoneurosis. When hysterical personality disorder present in addition, special aspects of management become necessary, described on pages 930-931.

Obsessional Neurosis

An *obsession* is a constantly recurring thought which the patient recognis as his own, but resists because it is foolish or repugnant. In spite of his effor to dismiss the thought, it persists in returning so that in the end he becom tormented by it. A *compulsion* is a similarly insistent urge to perform, or t repeat, some act which the patient consciously repudiates as meaningless o troublesome; he struggles against the urge, but finds himself experiencing ver acute anxiety, which is only allayed by his giving in and performing th compulsive act.

Obsessive-compulsive symptoms may occur as episodes of illness in otherwis normal individuals. They may become aggravated during an episode of psychological illness. Dr Samuel Johnson, for example, experienced spells of 'the touching mania' during his depressive illnesses. Sometimes obsessions and/or compulsions are the outstanding, if not the only, symptoms of which a patien complains. In this condition the patient, although perfectly lucid and in contact with his environment, may be severely handicapped by the unrelenting pressure of his unwelcome thoughts and impulses.

Aetiology. Obsessive-compulsive neurosis is often found in the children of parents who are similarly affected, but it is not clear whether this is due to transmission of a hereditary predisposition to the disorder. Many observers believe that the meticulous, rigid routine imposed by such parents is more conducive to obsessional neurosis in the child than the hereditary endowment itself.

Extrinsic factors, other than the influence of obsessive parents during the formative years, appear to contribute little to the causation of obsessional neurosis.

Clinical Features. Obsessions may be arbitrarily divided into (*a*) ideas; (*b*) impulses; (*c*) phobias; and (*d*) ruminations.

The *ideas* consist of thoughts, images (often obscene) and strings of words and phrases, which constantly recur to the patient despite his resistance to them, and his recognition that they are absurd and meaningless. The *impulses* are urges to some act such as killing offspring, or jumping under a train, or to less fearsome activities like laughing at sorrow or arranging objects in a certain manner. The *phobias* are fears of some act, and are often indistinguishable from impulses. They may, however, be separate, as when a phobia of knives develops from fear of an impulse to use them for murderous ends. Likewise, a patient may not be troubled by obscene thoughts, but rather by the fear that he may have such thoughts; he fills his mind with neutral thoughts lest obscenity should intrude. Obsessive phobias are distinguished from the phobic fears countered in anxiety states by the fact that phobic anxiety can be allayed by nply avoiding the object, or place, which provokes it, whereas the idea presenting an obsessive phobia keeps on invading the patient's consciousness. *uminations* comprise the practice of constantly turning over problems in the nd, seeking an answer to a question. Religious scruples are of this order, hen the patient has repeatedly to examine and re-examine his conscience, ncertain as to whether he has offended or not.

These symptoms are often intermingled one with another, and may be of l degrees of intensity. Sometimes they are merely a nuisance, not interfering riously with life, but preventing easy, enjoyable activity. In other cases they ecome so severe as to arrest all activity, and make the ordinary daily round n impossible task. Thus a patient, who was a house painter, stood for three ours, unable to paint over a crack on the wall until he had the 'right' thoughts n his mind. Another patient, a housewife, spent all her time washing her hands or fear they should be contaminated, and so was unable to do her housework.

When the obsessions are severe they cause great anxiety and tension, the patients becoming increasingly agitated as they fight against the compulsion. n addition, they frequently become depressed, since life becomes so difficult and escape from the obsessions seems to be impossible. Suicide is, however. relatively uncommon except in depressive phases.

Diagnosis. The diagnosis of obsessional neurosis does not present great difficulty providing there is adherence to the exact criteria of the definition given at the beginning of this section. There must be the feeling of compulsion and, most important, the patient must recognise it as senseless or absurd and resist it. Delusions must be distinguished from obsessions; the patient does not feel his delusions are silly, but firmly believes in their truth. Similarly, such schizophrenic symptoms as feelings of compulsion or direction by some unknown force should not be confused with those of the obsessive-compulsive, who knows that the thoughts and impulses, however unwelcome, are *his own* thoughts and impulses. When the severity of such symptoms shows very marked fluctuation, a co-existing recurrent depressive illness should be suspected.

Treatment. The obsessional neurotic does not respond well to treatment but often the condition is self-limiting, at least in its acute phases. The patient should be encouraged not to endeavour to overcome the obsessions by will-power; he should be assured that his doctor knows that his irrational, obscene or murderous thoughts are not indicative of his true nature. He should be encouraged to avoid situations which foster the development of the obsessions, and should diversify his interests as much as possible. The best antidote for obsessive ruminations is to keep the patient busy with practical tasks which demand his attention.

Personality Disorders

In every large community there are a number of people who do not conform to the prevailing norm. Statistically speaking, exceptionally gifted individuals are no less abnormal than the eccentric and the social misfits: but it is t latter who are more likely to come to medical attention.

The personality disorders began to gain notice only late during the develo ment of psychiatry as a medical discipline; they have been recognised increasing as the out-patient responsibilities of psychiatrists have extended, and as ps chiatric units have developed in general hospitals. The diagnostic differentiati between psychiatric illness and personality disorder is the more necessa because very often the two co-exist. Indeed, clinical convention has it th hysterical psychoneurosis commonly supervenes in individuals with hysteric personality, obsessional neurosis in those with obsessional personality disorder etc. In addition to their presentation with psychotic illnesses and psych neuroses, people with abnormal personalities often appear clinically wit psychosomatic disorders and may be chronic hospital attenders. Abnorma personalities may not enter the medical ambit at all, but be encountered i penal settings. Still others may continue unrecognised in the community an only escape anonymity when widespread screening of the population occur as in wartime when obligatory intake to the armed forces exposes all adult to clinical scrutiny.

The association between the different types of psychiatric illness and th various forms of abnormal personality is now recognised as a more complicate problem than the earlier statements of the position suggested.

The central feature of abnormal personality is some degree of persisten abnormality of behaviour which is frequently, but not necessarily, antisocia in its manifestations. The abnormality varies considerably in degree, ranging in severity from schizoid and hysterical people who are often valuable if somewhat unstable members of the community, to psychopaths who are socially destructive.

Obsessional Personality

The obsessional person gives scant regard to the emotional aspects of a situation or an interaction. He is rigid rather than flexible, overattentive to details rather than to the wider scope of an event or encounter, and prefers to have everything predictable and orderly. He often appears officious, sometimes so pedantically that he can be comical, and not only controls himself excessively but also attempts to dominate others. He appears to behave in an excessively egotistical manner, and responds in an overriding way when involved in a venture calling for co-operation. He is over-careful, methodical, liking things cut-and-dried, concerned with neatness and orderliness. He can be very meticulous, punctual and overorganised, to the extent of becoming uncomfortable and even upset if his routines are disturbed by any unexpected development. He has a set of fixed standards and points of view, from which he can deviate only with great difficulty. He is uninfluenced, therefore, by the wishes, needs, opinions or views of other people.

The meticulousness and preservation of sameness extends to the person's mode of dress, which can be scrupulously neat. He can be overconscientious, paying greatly excessive attention to minutiae. He may work compulsively, and be unable to make use of opportunities for relaxation. Such a person, in consequence, can be of particular usefulness in a bureaucratic post calling for upulous concern with details. He may be highly obstinate when faced by y requirement that he should deviate from his straight and narrow path.

At times such a person appears to leave some loophole, so that the con- rmity, inhibition and rigidity is waived in some context or other. The precise, at youngster, who must have everything in place, may for example permit mself to have his clothes cupboard in disorder, or may periodically forget rift to overspend in a foolish self-indulgence which rationally is at odds with s habitual miserliness.

The gross form of the disorder is easy to recognise. The milder forms may be ss obtrusive, and may be particularly evident only at times of pressure, as when n examination is looming for a youngster or when a house-proud woman has elatives coming to stay in her home.

Schizoid Personality

The schizoid person is essentially solitary. He is aloof in his loneliness, detached and distant from other people. He has few close relationships, and may be much more preoccupied with some impersonal activity in the realms of electronics, physics, mathematics or engineering. Often the engrossing venture is a personal fad or invention, which may be of negligible application in ordinary life, but may be pursued with a single-minded devotion inappropriate to a mere hobby or interest.

Cold, quiet and shy, the person's abnormality may already have been apparent early in childhood, from an inability or disinclination to mix, and a preference for solitary pursuits. The lack of friendships may have been upsetting to the parents; as the person grows up, he can himself be distressed by his incapacity for any intimacy in his associations with others.

The person may appear odd, eccentric, gawky, and in his awkward isolation may appear as a figure of fun. He may seem excessively secretive. Schizoid people are often solitary workers, who cannot function satisfactorily in a team. Bookish, reserved, out of touch with others, relatively blind to social cues, their personal lives may appear barren. However, this remote exterior may belie the strong emotions which some schizoid people cannot express. Others find a vehicle for their private feelings, and may keep a diary, or indulge in day-dreaming, or succeed in establishing some relationship in which the expression of emotion is allowed.

The schizoid person is at times mistrustful, seeing slights where none is intended. He is rigid and brittle. He has little empathy with other people, and so remains unaware of their intentions, feeling and wishes. When he attempts to appraise others intuitively, he is often wildly wrong, thereby complicating his already attenuated relationships. He can be made profoundly uncomfortable when well-meaning but misguided mentors or doctors attempt to have him mix more, or become intimate with another person, perhaps another isolate as lacking in interpersonal skills as himself.

Suspicion can become the prevailing response to others, the person believing that he is being exploited, misused or disparaged. Some clinicians would differentiate this development separately, diagnosing such a personality as paranoid.

Hysterical Personality

People of this type can be identified on the basis of a constellation behaviours: they seek to please and influence others; they crave attentio they are insincere; and they are given to excessive displays of emotion.

An hysterical person appears to be exploitative, with an eye always on t other person. She talks for effect, not to convey any honestly-felt intentio One feels her need for appreciation, and her readiness to express herself wi that aim in view. She plays up in order to evoke a response, and that respon is one which she has already ‘decided’ to elicit.

Psychiatrists probably over-diagnose this type in abnormal women, attachin the label very much less often to men. The person is showy, histrionic i manner and dress, with a quality of spuriousness and exaggeration, eve theatricality, in what she does. The exhibitionism appears intended to impre others, even to shock them. Speech is superficial, with plentiful hyperbol (‘heavenly’, ‘ghastly’), which only heightens the effect of shallowness. Wome of this type suffer from sexual timidity and frigidity, the more distressing t them because their frequently seductive manner and provocative dress invite advances with which they cannot cope; hysterical men also have difficulty i establishing a close relation with one woman, and may seek intimacy in a serie of attachments of short duration.

Sociopathy

The sociopath suffers from the most severe form of abnormal personality. Because of his serious defect in the capacity for feeling, he is often described as ‘affectionless’. Lacking in conscience he has great difficulty in realising that other people are harmed when he behaves antisocially. Loveless, indifferent and destructive, he cannot form satisfactory relationships, and major failures repeatedly occur in his marriage, his work and his social life. He comes into conflict with the norms, customs and laws of his community, not learning from his failures, however catastrophic; already present from an early age, his social ineptitude is persistent, leading him chronically to be in trouble. Many sociopaths are superficially likeable and charming, and initially mislead well-meaning people whom they subsequently disappoint and mortify.

Impulsiveness is usually evident, the sociopath dismaying those associated with him by uncontrolled, often destructive outbursts in the absence of sufficient provocation. Such precipitate and deplorable action has been spoken of as ‘short circuit reactions’, to indicate that often the person is aware of the build-up to the outburst, and will often admit that after the aggressive or destructive episode he feels calmer and relieved of tension.

The sociopath does not show ability to modify destructive behaviour reactions, or to learn from even drastic setbacks; he may be punished repeatedly for the same unacceptable behaviour, and yet continue it; the individual's antisocial patterns are often monotonously repetitive. Kleptomania, gambling, or physical assaults may each be associated with excitement which the sociopath seeks and indulges repeatedly; the antisocial behaviour can be seriously destructive to others, as in cases of sadistic attacks on children or of pyromania.

The lack of regard for the possible consequences of his actions is also impres- e, the sociopath appearing not to care about the outcome, and scant in his nsideration even of persons on whom his welfare depends. He disregards s obligations to others: it is on this account that the Mental Health Act ngland and Wales) of 1959 described the sociopath's conduct as 'seriously responsible'. The lack of concern amounts often to callousness.

His social relationships are shallow and transient. He is not loyal to individuals r to groups. He has poor judgement of situations, and often lies his way out of mplications. He is indifferent to the welfare of others. He requires immediate tisfactions, not being able to postpone gratifications; he seeks instant excite- ent or relief of discomfort, and may misuse drugs or alcohol so that secondary ddictions are common. Swindling and deception are frequent features.

Two types of sociopathy are distinguished:

Aggressive Sociopath. The hostility displayed in attacks on other people, damage to property, thefts and fraud may bring the sociopath to legal attention.

Passive Sociopath. A person of this type is seriously inadequate and cannot adapt to social requirements; he is chronically inept, passive and dependent. Many are placid and responsive; others are cold, withdrawn and apathetic. They may exist as aimless drifters, to be found in places where hobos congregate. Even if supported in a family or protective environment such as a half-way house or hostel, such people may be sufferers from drug addiction or alcoholism.

Management Implications

The chief medical relevance of personality disorder, in terms of the doctor-patient relationship, is that patients respond to the clinician in accordance with their particular personality deviation. For this reason, diagnosis of the personality type permits the doctor to plan management realistically, so that he does not expect a degree of co-operativeness which the patient is not equipped to provide. In addition, he will be better able to predict the patient's pattern of behaviour in the future.

For example, the long-term management of a patient with a hysterical personality disorder has much in common with that of a frightened or petulant child. It consists in convincing her that you are on her side, even while refusing to comply with some of her requests. Treating a patient with such a personality disorder is often a test of nerve; in the face of dramatic protestations and apparently alarming symptoms, one must quietly but firmly insist upon facing the painful realities from which the hysteric has taken flight. If one has succeeded in gaining her confidence, long-established symptoms will sometimes disappear with dramatic suddenness, but all too often they are replaced by others. The hysterical patient finds it difficult to abandon the defences against alarming feelings which she has been using since her early adolescence. In addition these patients are especially prone to develop an emotional dependence upon their doctor, which must be recognised and brought to their attention kindly but firmly. The family doctor can give helpful advice to other people in the patient's immediate environment, warning them that hysterical symptoms only beco aggravated if too much attention is paid to them, and encouraging them avoid entering into the hysteric's pattern of self-deception. It is usually mu easier for the onlookers than for the patient herself to see the real motivati of her symptoms, but of course, it is no use simply *telling* her—she has discover for herself why she behaves in the way she does.

The achievement of a long-term cure of an hysterical personality disorder a formidable task since it requires the emotional maturation of the patient. N surprisingly, both patients and their doctors often tacitly agree not to attem it. Instead, the doctor may concentrate upon dealing with the most pressin difficulties of the patient's immediate predicament and may settle for h remaining a somewhat demanding and dependent patient. In that case, th goal for each consultation can be to ensure that the patient departs calmer an with more self-esteem than when she arrived. The doctor helps the patien discover some modifiable aspect in a problem which she had considered insoluble

Alcoholism and Drug Addiction

Alcohol. Alcoholics are often brought reluctantly to their doctor by clos relatives who can see more clearly than the patient how seriously his life i being interfered with by his addiction. These unwilling patients are particularl difficult to treat; but the prospect is very different when the patient himsel is distressed by his abnormality and is anxious for change.

Addiction to drugs or to alcohol represents a form of psychological dependence and indicates that the patient has been unable to attain adequate satisfactions or self-esteem in his personal life. Addictions to drugs and to alcohol are associated with a high risk of suicide. The underlying lack of self-confidence is often so deep-seated that prolonged treatment and rehabilitation is necessary once the drug or alcohol has been given up. Alcoholism is a serious health problem in Britain, and more especially in Scotland. In 1968 mental disorders due to alcoholism were responsible for 26 per cent of male admissions to Scottish mental hospitals. It is an insidious condition, because the enjoyment of alcohol is socially accepted and even encouraged. The process by which an occasional drinker becomes an excessive drinker, and finally dependent on drink can be gradual; acquaintances, and even friends, are reluctant to draw attention to a man's excessive drinking because the alcoholic is notoriously liable to take offence. Here, however, doctors have a clear responsibility because often an intercurrent illness, chronic dyspepsia or haematemesis, or even a street accident will bring the patient to medical care, and a carefully taken history (especially if supplemented by information from others in the patient's family) will reveal the increasing dependence upon alcohol. Sometimes an unexpected hospital admission, interrupting a sustained high intake of spirits, results in the onset of *delirium tremens* which compels attention to the seriousness of the drinking problem. This is characterised by gross peripheral tremors, great restlessness, confusion, misidentification of people and places and delusional ideas. These delusions may be agreeable (as in the case of an alcoholic who sat cheerfully at the edge of his bed, convinced that he was engaged in trout fishing) but much more often they are threatening or even rifying, especially when accompanied by hallucinatory visions. Because of se complications, hospital admission may be necessary when starting to treat alcoholic.

Treatment of Alcohol Addiction. This consists initially of 'drying out', which ten calls for hospital admission. Withdrawal symptoms can be controlled by enothiazines, diazepam or haloperidol (p. 943). Parentrovite intravenously ay be of value. The next phase of treatment, once the patient is abstinent, is explore with him by means of a series of interviews, his personal and other roblems which need to be corrected. Psychiatric assistance is needed if obvious sychological disorder is apparent once the drinking has stopped. Those bstinent alcoholics who consider themselves in danger of relapse can ensure heir sobriety by taking Antabuse (disulfiram) 0·5 g daily, or Abstem (citrated alcium carbimide): when on these drugs, the patient will have an unpleasant eaction after taking only a small amount of alcohol.

The main requirement of treatment is that the alcoholic should become otally abstinent. Many alcoholics are active and valuable members of society nd can maintain this necessary abstinence if given appropriate medical supervision.

Morphine. Addiction is seen in doctors, nurses, pharmacists and dentists, and at times in patients who become addicted through therapeutic use. The desired euphoric effect can be achieved by subcutaneous injection, but as tolerance grows intravenous injections are used ('main lining'). Hypodermic tattooing of the skin, thrombosed veins and pinpoint pupils are indications of the condition.

Heroin. Addiction is increasing rapidly in incidence, and many addicts are young people. The drug has a marked euphoriant effect; it acts quickly and its desired action also dissipates quickly. The abstinence syndrome is particularly unpleasant. Many addicts cannot be cured, and their management then is by supplies of the smallest dose of the drug preventing the withdrawal symptoms, or by substitution of methadone in place of heroin.

Cocaine. Those addicted to cocaine take the drug in the form of snuff or intravenously. The most well-known toxic symptom is formication, the sensation of insects crawling under the skin. Use occurs mainly in those addicted also to heroin, the effect of cocaine alone being unsatisfactorily brief.

Lysergic Acid Diethylamide (LSD). This is used mainly by young people. Taken by mouth, it has dramatic effects lasting about six hours. Illusions occur, colour is intensified, mood changes include euphoria, awe or anxiety, a curious blurring between the individual and his environment is experienced, and phantasy thoughts, flight of ideas and delusions serve to heighten the mystical nature of the 'trip'. Proponents of the drug as a 'mind expander' sometimes overlook the serious hazards; these include psychotic reactions with paranoid delusions which can last many weeks, and non-psychotic reactions chiefly terror; both can result in self-injury or suicide. A bad LSD experience can be cut short by chlorpromazine.

Cannabis (hashish, marihuana, 'pot'). This is also used very commonly the young, sometimes only a few times; there is no evidence that occasion use is harmful. At first the user feels 'high', and then drifts into a peacef drowsy state heightened by unusual mental images. Skin flushing, rapid pul and dilated pupils may convey that a person has taken cannabis, usually smoking a 'reefer'. Many addicts use more than one drug.

Barbiturate. Many middle-aged or elderly women come to rely upon a nightl dose of sleeping tablets and some of them find that if they take two or thre during the day, this helps to calm their nerves. Gradually, they begin to sho the signs of chronic barbiturate over-dosage: slight ataxia, absent-mindednes amounting at times to confusion as to time and place, slurred speech and tremo of the fingers. A sudden cessation of barbiturates can be followed by a majo epileptic fit. A patient cured of one addiction, e.g. alcoholism, may start usin another drug, e.g. barbiturate, which he erroneously regards as innocuous.

Amphetamine. This drug, formerly used in the treatment of obesity and malnutrition, soon came to be abused, particularly by teenagers, either alone or combined with barbiturate ('purple hearts') to provide a rapid lifting of the spirits and feeling of euphoria. The use of amphetamine readily gives rise to a psychological dependency and also to an acute psychotic reaction with auditory and visual hallucinations and delusions of persecution. These features can be clinically indistinguishable from those of paranoid schizophrenia, but they clear up in about three weeks time after withdrawal of the drug.

Sexual Deviation

Sexual deviants are people who are unable to obtain physical and emotional satisfaction in normal sexual intercourse, but can do so only in ways which to a greater or less degree are socially condemned. Practices which alarm, threaten or injure other persons, such as exhibitionism, paederasty (having sex with immature partners of either sex) or sadism (deriving sexual pleasure from inflicting pain) are still regarded as antisocial and are punishable by law. On the other hand, public opinion has become somewhat more tolerant of abnormal practices which do not interfere with other people. This change of opinion found expression in the Sexual Offences Act, 1967, which, for the first time in British history, excluded homosexual acts, carried out in private by consenting adults, from any legal sanction.

Most forms of deviant sexual behaviour, such as homosexuality, transvestism (deriving gratification from wearing the clothing of the opposite sex) and fetishism (in which the presence of some object, such as an article of clothing, becomes essential for sexual excitement to take place) seem to be the result of distorted experiences at the stage of development when boys and girls learn their sexual role. These deviant forms of gratification often prove very resistant to change. If the patient suffers because of them—and many sexual deviants appear to be rather content with their lot—treatment often has to be limited to damping down the intensity of the sexual drive, e.g. by the administration estrogens, or to helping the patient (and perhaps also his spouse) to accept peculiarity.

Psychosomatic Disorders

it has long been an axiom in medicine that not only the disease must be ated but also the patient. There are patients whose symptoms are limited the mental sphere and who have an obvious neurotic or psychotic disorder, d there are patients whose illness appears to be the result solely of physical sease, such as neoplasm or infection. Between these two extremes there are wever many patients who show not only physical symptoms and signs but ychological disturbances as well. In some cases a recognisable physical disease ecedes the psychological changes, as for instance the depression and hopelessess which may be seen in a patient who realises he is dying from an incurable ew growth, but in others emotional disturbances and physical symptoms and gns occur together without any primary physical disease to account for them. xamples of such conditions are peptic ulcer, bronchial asthma, various forms f dermatitis and colitis, and these are called psychosomatic disorders. The nplication of this term is that tension arising from a long-standing emotional onflict can induce changes in bodily function (e.g. excessive secretion of gastric uice, spasm of bronchiolar musculature) which, when repeated over a period of ime, can in turn lead to actual tissue damage.

For many years, attempts have been made to delineate particular personality ypes associated with different forms of psychosomatic illness. A review of this iterature, however, reveals the recurrence in very diverse contexts, of relatively few emotional elements, the chief of which are dependency, anger, fear, which appear to be most harmful when they are denied conscious expression. Repressed dependency needs have been particularly associated with peptic ulcer and colitis, repressed anger with asthma and hypertension. Individual cases, however, when studied in depth, are not easily fitted into any common mould. Modern psychosomatic theory has, therefore, retreated to the more general observation that all psychosomatic patients have long-standing problems in the control of their own internal emotional homeostasis, and in the conduct of their relationships with people who matter in their private lives.

Each individual is equipped with the memory-store of a lifetime of previous experiences and emotionally-charged perceptions of things, events and especially people in his environment. Stresses, both physical and emotional, are encountered by all of us. Our ability to surmount them depends partly on our inheritance and partly on our several life-histories. Traumatic experiences during crucial stages of early development leave us predisposed both to neurosis and to psychosomatic illness; it is probable that genetic factors, which have endowed some of us with a particularly vulnerable organ or organ system, will dictate both the occurrence of a psychosomatic illness (which often indeed co-exists with neurotic symptoms) and the choice of the organ which is affected.

Treatment of the emotional disturbance and disregard of the local physical factors, or vice versa, will seldom lead to benefit for the patient, and an assessment must be made in each case of the relative importance of these two factors, so that whichever appears to have the greater aetiological significance can be the main target for therapy. The general practitioner is often in the best position to know the unrealised ambitions, the frustrations at work or at home, or the marital unhappiness which may form the background to the patient's illness. A knowledge of the family history may also reveal important hereditary predisposition, as in migraine, for example, which plays a part in determining the physical form of the illness.

Functional Psychoses

Depressive Illness

Depression is a mood which all of us experience from time to time, usually as a result of some distressing circumstance. There are however many patients who attend their doctors seeking relief for a large number of symptoms loosely grouped under the term 'depressive illness'. Some may complain of feeling unduly depressed following some unhappy experience, while others clearly have neuroses of long standing. Many patients are unaware of being depressed, but report feelings of exhaustion or vague aches and pains, and attribute their low spirits to these physical ailments. Yet others, although looking a picture of misery, do not complain of being depressed, but stress only their own wickedness and unworthiness.

Clinical Features. From the many patients suffering from 'depression' it is important to separate a group who have certain features in common—important because these patients can often be cured quite rapidly and because, if left untreated, they are the most likely to commit suicide. The clinical features shown by this group, in addition to a mood varying from mild depression to black despair are: insomnia of a type characterised by early waking after two to three hours sleep; diurnal variation of mood, in which the depression often lifts considerably towards evening; slowness of thought, and inability to make decisions; ideas of guilt, unworthiness and self-blame which are often delusional in intensity, i.e. they are impervious to reasoned argument or demonstration of their falsity; and various somatic manifestations such as loss of appetite, loss of weight, amenorrhoea, occipital pressure headache, backache, constipation, retardation of physical activity (more rarely aimless over-activity or agitation), and hypochondriacal delusions. Such a patient may sit bowed and immobile on the edge of a chair obviously in the depths of misery, weeping silently, wringing his hands and answering questions in slow monosyllables; but in the earlier stages the physical appearance is less striking and the diagnosis depends on the doctor's ability to elicit the symptoms described above.

Such patients are suffering from *endogenous depressive illness*, known in earlier times as melancholia or 'the spleen'. They are often people who have been subject previously to mood swings or people who have overscrupulous, rigid personalities following too strict upbringing and who develop depression particularly in later middle age (involutional melancholia). Endogenous depressive illness may be precipitated by physical diseases such as influenza, pyelonephritis and infective hepatitis, and may sometimes be the first symptom of cerebral disease, such as general paresis or cerebral atherosclerosis, but more often, as its name suggests, it arises without detectable external influences. Endogenous depressive illness is commoner in patients of middle age or older.

Other forms of depressive illness, sometimes called *reactive depression*, may be seen in younger or middle-aged people, many of whom show concomitant symptoms of anxiety neurosis rather than the symptoms described above. When there is insomnia it usually takes the form of inability to get to sleep without the early waking characteristic of endogenous depression, and such patients often feel better in company in contrast to the sufferer from endogenous depressive illness, who finds meeting people a painful ordeal and prefers to suffer alone. It must be remembered that both profound, endogenous illness and also relatively less serious reactive depressive illness may be precipitated by external events, particularly those which impart a sense of loss, separation or disappointment. The difference in their manifestations is largely a matter of the intensity of the suffering involved, but some very depressed patients are prevented, by the illness itself, from revealing the full extent of their suffering. Their self-deprecation and sense of unworthiness may make them believe that they deserve to suffer and their feelings of guilt may make them reluctant to disclose the full intensity of their feelings. Many severely depressed patients are afraid that they are 'going mad', and many are frightened, as well as ashamed, at their own suicidal thoughts. Some doctors, out of a mistaken fear of adding to their distress, may connive in these patients' attempts to avoid mentioning these painful topics; but in fact, so far from harming the very distressed patient, it often brings a measure of solace if he is helped to give expression to these deep-seated fears. One should not, therefore, hesitate to help him put them into words. The fear of insanity can often be relieved by a frank discussion of the illness, accepting its severity but indicating its likely favourable outcome; thoughts of suicide have to be evaluated differently according to whether they have been fleeting and resisted, or constant and insistent.

Treatment. The first task in treating depression is to consider whether it is the consequence of the patient's painful circumstances or of some other illness, in which case it is the life-situation or the illness which must receive attention. In true 'endogenous depression', however, the depression of mood, sleeplessness, loss of energy and loss of weight are out of proportion to any precipitating factors which may be elicited. In such cases it is best to proceed without delay to treat the patient with one of the potent antidepressant drugs (p. 945). One has to bear in mind, however, that these drugs do not take effect until after some 6 to 14 days.

Severe depressive illness, especially when associated with restlessness and agitation, with delusions of unworthiness and preoccupation with thoughts of death, is an extremely distressing condition and fraught with risks of suicide, especially when the patient states that his mind has been dwelling upon a particular method of killing himself. Such cases should be admitted to psychiatric care in hospital, where electric shock therapy, administered under intravenous anaesthesia and modified by muscle-relaxant drugs, is often still indicated, because this is the speediest way to relieve the patient's suffering.

As a general rule, it is wise to postpone any practical decisions about business, change of work or domestic matters until the patient has regained his normal frame of mind. Once the patient's mood has responded to physical method of treatment, it is essential to review his personal circumstances with him an to help him make plans to cope with the difficulties which may have precipitate his illness.

Schizophrenia

Schizophrenia is the illness whose symptoms correspond most closely to th popular conception of the madman. These patients are likely, at least during the acute phase of their illness, to experience hallucinations (most commonly in the form of threatening or unfriendly voices) and to express bizarre delusions with little or no appreciation of why it is that their ideas are unacceptable t those around them. Both delusions and hallucinations may occur in other forms of mental illness, such as severe depression, mania or delirium, bu certain features are especially suggestive of schizophrenia. These include (1) *passivity feelings*, in which the patient is convinced that his actions are controlled by some alien power, (2) *thought insertion* and *thought broadcasting*, in which he feels that other people put thoughts into his mind, and are able to read his thoughts and (3) *paranoid delusions* in which he believes that he is surrounded by hostile forces which watch him and secretly intervene to do him harm. Patients with depressive illness may also develop paranoid ideas, but these are coloured by their all-pervading feelings of guilt. For example, a depressed patient may believe that he is being watched by secret police because they have found out that he has committed a terrible crime. The paranoid schizophrenic, on the other hand, is quite sure that it is his unseen enemies who are the villains of the piece, and he their innocent victim. These patients, unfortunately, tend to have little insight into the fact that they are ill and in need of treatment. As a result, when their behaviour is becoming alarming or threatening towards their neighbours, it may be necessary to consult a psychiatrist and arrange for them to be admitted compulsorily by means of an emergency order (signed by one doctor) or a formal certificate (signed by a psychiatrist and by the patient's own physician). In England and Wales this certificate is itself sufficient authority for the compulsory treatment of a mentally ill patient; in Scotland, the authority for such treatment is given by a Sheriff, after reading the two doctors' reports. In both countries, the patient's state must be reviewed after 28 days, and in many cases it is found no longer necessary to detain him 'on order'.

These are the more florid manifestations of schizophrenia. Milder signs are less easy to recognise, because they merge into the peculiarities of everyday living. These include instances of unexpected rudeness or tactlessness, abrupt and inexplicable behaviour with a marked withdrawal from ordinary social contacts. Such persons may be considered awkward or unsociable and it is only when they reveal quite bizarre ideas, shout back at their hallucinatory voices, or otherwise behave in a conspicuously strange manner, that one realises that they are not merely eccentric, but mentally ill.

Treatment. The advent of the phenothiazine drugs (p. 944) has very significantly changed the prognosis of schizophrenia but it should be remembered that even before there was any specific drug treatment for this illness, many cases made a spontaneous recovery from the acute stage of the psychosis in the course of three to nine months. Even now, the new drugs offer symptomatic relief of the patient's delusions, hallucinations and alienation from reality, rather than a radical cure of this little-understood disease. There is abundant evidence that the way in which the patient is treated, both in hospital and in the community, will influence both his degree of recovery and the probability of a subsequent relapse.

Putting it briefly, it may be said that schizophrenic patients do badly if they are allowed to withdraw too completely from social contacts and practical activities; but they also do badly if they are involved in emotionally demanding relationships, to which they are unable to respond. Many, if not most, schizophrenics must be regarded as having particularly vulnerable personalities and many emerge from the acute stage of their illness with some residual defects ('end states'). They are best able to cope with their handicap if they can be helped to come to terms with their limitations. These patients are not necessarily intellectually impaired—they may be highly intelligent—but they are seldom able to cope with positions of responsibility, particularly when they are required to supervise, or interact with other people. Hence, they do best in tasks in which they can work on their own, with only rather formal contacts with their fellows.

In recent years, the psychiatric hospitals have discharged the great majority of their schizophrenic patients back to the community and to the care of their general practitioners. The latter can best help them by ensuring that the patients take their prescribed course of drugs for at least the first year or two after discharge. Long-acting phenothiazines, such as fluphenazine ethanate (Moditen) and fluphenazine decanoate (Modecate) can be given by injection each two to four weeks; an anti-Parkinsonian drug is then also needed. The doctor should be ready to enlist the help of a Mental Health Officer or a social worker if his patients appear to be having difficulties either at work or in their domestic relationships.

Organic Psychoses

Psychiatric symptoms may arise in the course of physical illnesses which either primarily or secondarily affect the brain. The occurrence of delirium during the course of febrile illnesses or the mental symptoms of general paresis are two well-known examples. It is important to recognise certain mental symptoms which occur in organic mental syndromes, since their presence should lead to the search for physical factors which may not otherwise have declared themselves. The organic psychoses can be divided into two groups: *delirium*, which is an acute disorder, and *dementia*, which is a chronic disorder. Generally speaking the acute form is potentially recoverable, being the result of temporary effects on the brain from toxic processes or disorders of metabolism, while the chronic form is the expression of more severe and progressive tissue changes in the brain and is thus less amenable to treatment. The mental symptoms of each of these organic syndromes are not specific to the causative disease and will be the same whatever may be the underlying physical disorder producing the delirium or dementia.

Delirium

This acute syndrome may be produced by such varied conditions as dru intoxication (alcoholism, LSD), infections (encephalitis, smallpox, typhoi fever), trauma to the brain, electrolyte imbalance and metabolic disorder (hepatic failure, uraemia), vitamin deficiency (Wernicke's encephalopathy) and cerebral hypoxia (heart failure). In addition to the physical symptom appropriate to the disorder in question there are often found slurred speech tremor, nystagmus, diplopia and sluggish pupillary reactions. The characteristi mental symptoms are: insomnia and restlessness; disorientation; impairmen of memory and of ability to grasp the significance of a situation; hallucinations particularly in the visual sphere; ideas of persecution (paranoid ideas); and a feeling of fear or terror. All the symptoms and particularly the level of consciousness are variable. The patient when undisturbed may appear deeply asleep, but quite weak stimuli may rouse him to a state of restlessness varying from simple tossing and turning to such activities as aimless searching in the bedclothes or repeated carrying out of motions associated with his occupation. He may appear orientated for time and space and be able to recognise visitors at one moment, only to be quite confused soon after. The patient will often give the easiest answer to a question without regard to the truth and may supplement his faulty memory and perception by invention (confabulation), as when he describes in detail a large meal which he says he has just had, when in fact he has eaten nothing. Visual hallucinations are characteristic of delirium, and are usually vivid and may be terrifying. Many are based on illusional misinterpretations of objects seen in the room; thus patterns on the wallpaper may become an advancing army of hideous and menacing reptiles. Hallucinations of other senses may occur. Doubt and suspicion are readily induced by the impaired mentality leading to misinterpretations and may blossom for a short time into transient and rather ill-defined delusions of persecution. Such an acute organic syndrome is commonly precipitated by withdrawal of alcohol or of barbiturates, from patients who have become habituated to taking them in substantial amounts. When the syndrome is due to alcoholism it is known as delirium tremens, but its features do not greatly differ from those of delirium from other causes.

The course and prognosis of delirium depend, of course, on the underlying physical disease, and treatment of this in most cases clears up the mental symptoms completely. Sometimes, however, delirium may be an episode in a progressive dementia or the herald of a serious psychosis.

Treatment. The use of intramuscular injections of chlorpromazine has transformed the management of acute delirium, enabling the majority of patients to be cared for in a side-room of the medical or surgical ward where their primary disease is being treated. In all these conditions the patient can be helped by explanations and friendly support; patients who are frightened and bewildered tend to regress to a state of childlike dependency and welcome a firm reassurance from someone whom they are willing to trust. They cannot, however, be kept calm if staff changes expose them to many strange faces or if they are bewildered by too many novel events. Some patients have catastrophic actions following operations on the eyes, when they must submit to being indfolded for some time, and others have reacted adversely to the accompaniments of cardiac resuscitation or renal dialysis. These acute psychoses contain n element of panic.

Dementia

This chronic organic syndrome may be caused by a wide variety of diseases f the brain. The most common of these is cerebral atherosclerosis, and other nportant causes include cerebral trauma, inflammations (neurosyphilis, enephalitis), disseminated sclerosis, intoxications and deficiency disorders (chronic lcoholism, pellagra, vitamin B_{12} deficiency), prolonged hypoglycaemia, carbon nonoxide poisoning, cerebral neoplasm, and a group of degenerative disorders ncluding Huntington's chorea and senile dementia. It will be seen that some f these conditions (encephalitis, alcoholism, vitamin deficiencies) may also ause delirium. The cerebral changes brought about at first by these factors esult in delirium and can be reversed by treatment, but if they are allowed to ontinue unchecked too long, permanent cerebral damage occurs, giving rise o dementia.

The clinical picture of dementia varies to some extent with the cause, the previous personality of the patient, the age of onset, and the rate of progression, but in all cases the mental symptoms are seen to involve the intellect, memory, emotions and behaviour, although the actual degree of impairment depends on the factors mentioned above. Insomnia is often an early symptom and may lead to nocturnal restlessness and confusion as the disease advances. Judgement and reasoning are involved early, and the disability caused by this will depend on the extent to which these faculties are utilised in the patient's daily life and work; it will be more noticeable in a barrister than in an unskilled labourer. Impairment of memory is the most prominent finding, particularly in relation to recent events, and in the later stages this may combine with defective perception to produce disorientation in space and time. Impairment of higher control leads to emotional instability and outbursts of violence or sexual aberrations at variance with the patient's previous character. There may be wide fluctuations of mood with euphoria or depression but finally, as mood flattens, the patient sinks into apathy. Delusions are common, and may be either centred on the patient himself, when they are grandiose or self-condemnatory and hypochondrial according to the mood, or centred on others, when they tend to be paranoid. As the structure of the personality disintegrates, the patient neglects his appearance, becomes lax in personal cleanliness, and careless incontinence occurs. Focal neurological signs may be found, e.g. dysphagia, apraxia, agnosia, hemiplegia, and epileptic attacks, either focal or generalised.

Psychiatric Disorders in the Elderly

In today's medical practice, the care of the elderly is playing an increasingly large part. Geriatricians and family doctors have learned to cope with the multiple minor ailments and chronic handicaps which beset old age. In the realm of psychiatry, too, it has been increasingly realised that old people d not merely suffer from progressive loss of memory and intellectual power Even those who show signs of cerebral atherosclerosis, with a succession o minor cerebrovascular accidents, often show fluctuations in their mental capabilities and at times they are themselves acutely aware of the reduction in thei mental and physical powers and become correspondingly depressed. Sever depressive illness is common in the elderly and this responds well to activ antidepressant treatment. What is not so widely appreciated, however, is th fact that episodes of neurotic illness, with anxiety states, phobias, hysterica symptoms or compulsions are also encountered in this age group, and are no less amenable to simple psychotherapy than at other ages. In the after-care o these older patients it is important to remember that social isolation is an important threat to their mental well-being. This becomes even more importan when physical disability or deafness further restricts their opportunities o making contact with other people. Here voluntary agencies as well as local authority welfare and preventive services can do useful prophylactic work, but the family doctor is often in the best position to recognise when an ageing (and perhaps recently bereaved) patient is in especial need of such help.

Elderly patients easily develop delirium, and then adapt poorly to sudden changes of scene and bewildering happenings. It is helpful for them if they can be visited by only a few nurses and doctors who take pains to identify themselves; their sick-room should be well lit and they should be encouraged to keep a few treasured possessions on their bed-side table. Since patients with even very slight clouding of consciousness are prone to misunderstand what is happening round about them, any changes of routine or new procedures should be explained to them in advance, in simple terms and if necessary more than once.

The Uses and Misuses of Psychotropic Drugs

The consideration of the details of drug treatment in psychiatric disorder is kept to the end of this chapter in order to guard against the misleading idea (which pharmaceutical advertising literature is only too ready to convey) that for every psychiatric syndrome there is a specific medicinal remedy. Used wisely, psychotropic drugs can do a great deal to reduce the distress of psychiatrically disturbed patients, but it has to be remembered that they are palliative and not curative remedies, and also that they can be dangerous if misused. During the past 20 years, one of the most striking changes in morbidity in Britain as in other advanced societies, has been a conspicuous increase in the incidence of attempted suicide, particularly cases of self-poisoning (p. 947). More than 80 per cent of these patients had swallowed overdoses of medicines prescribed by a doctor, the most common classes of drug being the barbiturates, the tranquillisers and the antidepressants. These figures can be variously interpreted, but they demonstrate very clearly the danger of relying upon drugs to solve the problems of emotionally disturbed patients.

No attempt has been made in this chapter to discuss all the psychotropic drugs, of which new variants are being introduced every year. However, Table 13 gives the pharmacopoeial and trade names and usual doses of drugs in the principal categories which have been frequently recommended.

TABLE 13

Summary of Psychotropic Drugs

Designation	Dose Range (in 24 hours)	Trade Name
Sedatives		
Chloral hydrate preparations		
Dichloralphenazone	650 mg tabs—one or two at night	Welldorm
Barbiturates		
Amylobarbitone sodium	60 mg tabs—one to three	Sodium Amytal
Butobarbitone	100 mg tabs—one or two at night	Soneryl
Quinalbarbitone sodium	50 mg tabs—one or two at night	Seconal
Pentobarbitone sodium	50 mg capsules—one or two at night	Nembutal
Phenobarbitone	30 and 60 mg tabs—30-120 mg at night	Luminal
Benzodiazepine derivative		
Nitrazepam	5 mg tabs—5-10 mg at night	Mogadon
Methaqualone		
Methaqualone	250 mg tabs—one at night	Melsedin
Methaqualone with diphenhydramine (25 mg)	250 mg tabs—one at night	Mandrax
Tranquillisers		
Phenothiazines		
Chlorpromazine	50-150 mg daily *	Largactil
Thioridazine	50-150 mg daily *	Melleril
Promazine	50-250 mg daily	Sparine
Trifluoperazine	3-12 mg daily	Stelazine
Prochlorperazine	10-15 mg daily	Stemetil
Butyrophenones		
Haloperidol	4·5-13·5 mg daily	Serenace
Benzodiazepines		
Chlordiazepoxide	10-60 mg daily	Librium
Diazepam	6-40 mg daily	Valium
Oxazepam	45-90 mg daily	Serenid-D
Meprobamate	400-1,200 mg	Equanil Miltown
Antidepressants		
Tricyclic Drugs		
Imipramine	75-225 mg daily	Tofranil
Trimipramine	75-225 mg daily	Surmontil
Amitriptyline	75-225 mg daily	Tryptizol
Monoamine Oxidase Inhibitors		
Phenelzine	45-90 mg daily	Nardil
Mebanazine	5-30 mg daily	Actomol
Tranylcypromine	10-20 mg daily	Parnate

* Larger doses of this drug are used in the treatment of schizophrenia (see text).

Hypnotics. The drugs which are most commonly misused are barbiturat sleeping tablets either alone or in combination with amphetamine (p. 934 EEG studies have shown that when normal subjects take as little as 200 mg o sodium amylobarbitone nightly for one week and then stop, their sleep patter remains disturbed for several nights before reverting to normal. Patients who have become dependent on sleeping tablets have some justification for being reluctant to do without them, because they will be very likely to experience broken sleep and troubled dreams for up to two weeks before they can re establish a natural sleep routine. Unfortunately, few drugs provide as effective sedation as do the barbiturates. Chloral hydrate is of particular value for elderly patients. The sedative nitrazepam has the merit of being remarkably safe. The best policy is to regard insomnia as the symptom of some underlying disturbance and to restrict its treatment to short courses, emphasising to the patient that it is preferable, in the long run, to tolerate a number of sleepless nights rather than to become dependent on a habit-forming drug.

Tranquillisers. Tranquillisers are drugs which allay a variety of symptoms, such as acute anxiety, restlessness, agitation, without sedating the patient, who remains alert and in touch with his surroundings but is no longer oppressed by his symptoms. There are four main categories of tranquillisers:

1. The *phenothiazines*, e.g. chlorpromazine, thioridazine; 2. The *butyrophenones*, e.g. haloperidol; 3. The *benzodiazepines*, e.g. chlordiazepoxide, diazepam, oxazepam; 4. *Meprobamate*.

The phenothiazines are principally used in the treatment of schizophrenia but may give rise to the symptoms of Parkinsonism. Chlorpromazine and thioridazine are in general use, 150-1,000 mg being given each day in divided doses during the acute stage of the illness. A suitable maintenance dose for a schizophrenic in remission is 100 mg three times a day. Chlorpromazine is also given by intramuscular injections (50-100 mg) in order to control states of delirium or over-excitement. An important side-effect to remember is its tendency to lower the blood-pressure; patients should be warned against the occurrence of moments of dizziness when they get up quickly from a sitting position. Because this tendency is more marked with elderly patients, they should be given smaller doses.

The *diazepines*, particularly diazepam 6-40 mg daily and chlordiazepoxide 10-60 mg daily which relieve the distress of acute anxiety, and *meprobamate* 400-1,200 mg daily can be used to give symptomatic relief to patients whose anxiety is accompanied by feeling 'keyed up' and unable to relax. Small doses of chlorpromazine or thioridazine (up to 150 mg daily) can also be used for this purpose.

The latter drugs can be particularly helpful in tiding a neurotic patient with anxiety over an especially difficult period of subjective distress. They do not, however, do anything to resolve the causes of the patient's symptoms, and unless this is altered either through psychotherapy or through a significant change in his personal circumstances, the symptoms will tend to recur and the patient may find himself becoming dependent on his palliative drug.

Antidepressants. There are two principal groups of antidepressant drugs:

1. *Tricyclic drugs* (e.g. imipramine, amitriptyline and trimipramine).
2. The *monoamine oxidase inhibitors* (e.g. phenelzine, mebanazine and tranylcypromine).

1. Tricyclic drugs are indicated for the treatment of severe depression of the ndogenous type, with symptoms of disturbance of sleep, appetite and energy. n order to be effective, they have to be given in sufficient dosage, which may e from 50 to 75 mg three times a day. Tricyclic drugs give rise to some disagreeable side-effects. Imipramine may make the patient feel even more on dge and restless during the first few days, and it may also cause some difficulty n micturition. These drugs have an atropine-like effect on the eyes, causing ifficulty in focussing. Amitriptyline tends to make some patients feel uncomfortably drowsy, and causes dryness of the mouth. These side-effects usually ecede with continued use and become quite easily tolerated once the patient egins to experience a lifting of his mood and a return of his former energy, which usually becomes apparent after 6 to 10 days. A course of these drugs hould be taken for three to six months, because if they are stopped too soon he symptoms of depression may recur.

2. Psychiatrists are themselves in dispute over the effectiveness of the monoamine oxidase inhibitor (MAOI) drugs. Controlled trials have shown them to be much less effective than either imipramine or amitriptyline in the treatment of severe depression, but some workers have claimed that they are especially helpful in the treatment of milder 'atypical' depressions or prolonged phobic symptoms, occurring in patients with good previous personalities. The action of MAOI drugs is associated with an accumulation of catecholamines in the brain and other tissues of the body; hence patients should be warned not to partake of substances rich in tyramine (such as cheese, Bovril, Oxo or Marmite, chianti and some types of beer) because these may interact with the drug to provoke a hypertensive crisis, with splitting headaches and a risk of subarachnoid haemorrhage. The MAOI drugs also potentiate other drugs, including pethidine, opiates, barbiturates, phenothiazines, amphetamine and alcohol, all of which should be avoided while a patient is taking this form of antidepressant.

Mention must also be made of the treatment of manic-depressive illness with *lithium carbonate*. The evidence is that lithium is effective in controlling mania; it may also prevent the recurrence of manic attacks when used as maintenance therapy.

Endogenous depressive illness, once of gloomy prognosis, is now eminently treatable, and with appropriate care few such patients become chronic hospital inmates any longer.

G. M. Carstairs.
H. J. Walton.

Further reading:

Anderson, E. W. & Trethowen, W. H. (1973). *Psychiatry*, 3rd ed. London: Baillière, Tindall and Cassell.

Forrest, A. (Ed.) (1973). *Companion to Psychiatric Studies.* 2 vols. Edinburgh a London: Churchill Livingstone.

Henderson, D. K. & Gillespie, R. D. (1969). *Textbook of Psychiatry*, 10th ed. Londo Oxford University Press.

Slater, E. & Roth, M. (1970). *Clinical Psychiatry*, 3rd ed. London: Baillière, Tind and Cassell.

The Non-medical Use of Drugs. (1971). Interim Report of the Canadian Government Commission of Inquiry. Harmondsworth: Penguin Books.

Acute Poisoning

ACUTE poisoning presents a very common and urgent medical problem. Its incidence is steadily rising and now at least 10 per cent of all adult emergency admissions to hospitals in Britain are suffering from poisoning (Fig. 97). Accidental poisoning in the home is also very common, especially in young hildren. A major factor in this rise in poisoning is the increased prescribing and therefore availability of drugs which all too often are carelessly left within reach of the toddler or provide the means for the impulsive overdosage. On the other hand, due to strict controls, the rate of poisoning in industry and agriculture remains low despite the introduction of many and varied toxic substances. The deaths in Britain from all forms of poisoning amount to about 6,000 per annum, a figure approximating to the number of deaths from road accidents.

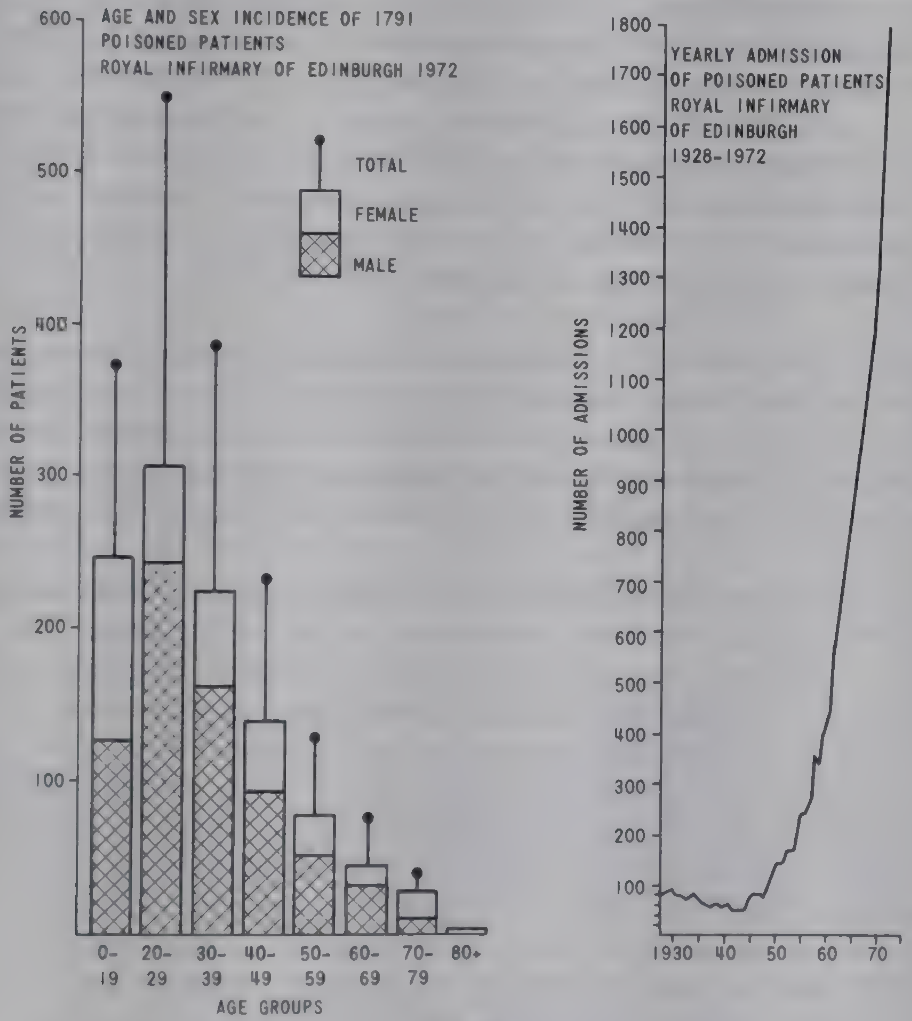


FIG. 97

AGE AND SEX INCIDENCE AND ANNUAL ADMISSION RATE OF POISONED PATIENTS TO ROYAL INFIRMARY OF EDINBURGH

This chapter deals with the clinical features, diagnosis and management o acute poisoning. Food poisoning is discussed on pages 71-74. Only brie reference is made to industrial and agricultural poisons and none to poisonin by ionising radiation.

Classification of Acute Poisoning

Acute poisoning can be described as either accidental or intentional.

Accidental Poisoning. Death from accidental poisoning has increased almost threefold in the past 30 years, women being more likely than men to die in this way. The frequency rate of accidental poisoning for Scotland is the highest in Europe and shows no sex difference. However, except in children it is doubtful if the official statistics reflect the true incidence of accidental poisoning. For example, it is difficult to believe the official statistics that more adults die each year from accidental barbiturate poisoning than from suicidal poisoning by these drugs. Inaccurate certification is the most likely reason for the large numbers apparently dying from accidental poisoning.

SUBSTANCES INVOLVED IN ACCIDENTAL POISONING. Death from accidental poisoning is the result most commonly of (*a*) carbon monoxide inhalation from domestic gas or fumes of incomplete combustion from stoves or motor car exhaust pipes, or (*b*) ingestion by children of household substances (e.g. paraffin or bleach), medicines (e.g. aspirin or iron tablets) and, rarely, poisonous berries.

Intentional Poisoning. This covers a broad spectrum of causes ranging from a minority of patients who are determined on self-destruction, i.e. 'suicidal poisoning', to a large group who until recently have been designated 'attempted suicidal poisoning' but who are more accurately described as indulging in 'self-poisoning'. The term 'attempted suicide' is best discarded as it implies a motive to an act of self-administered poisoning, which is frequently incorrect. The majority of people who deliberately take poison do not wish to die; in fact, they often take steps to ensure that measures to bring about their recovery will be available. 'Self-poisoning' is usually a conscious, often impulsive act, undertaken to manipulate a situation or a person to secure redress of circumstances which have become intolerable. Frequently relatives and society rally to the help of the unfortunate victim and the situation which has caused so much distress is rectified. Mistakes, however, do occur through misjudgement of dosage or of a failure to ensure that help would be to hand, and an act which was committed merely to draw attention to a particular situation may end in death. Self-poisoning often occurs in a setting of poverty and alcoholism and with a background of a broken home in childhood. The alarming increase in the incidence of acute poisoning is largely due to self-poisoning which accounts for approximately 90 per cent of all adult poisoned patients admitted to hospitals. This type of behaviour is commoner in countries which enjoy a highly developed welfare state and now constitutes a major social problem.

Under the heading of intentional poisoning, in addition to suicidal and self-poisoning, homicidal poisoning must also be included.

SUBSTANCES AND METHODS USED IN INTENTIONAL POISONING. *Self-poisoning.* Almost any substance may be taken for self-poisoning, but during recent years there has been a change in the type of drug used. Statistics from the Regional Poisoning Treatment Centre of the Royal Infirmary, Edinburgh, show that whereas seven years ago 60 per cent of admissions were due to barbiturate poisoning, this figure is now only 20 per cent. Their place has been taken by non-barbiturate hypnotics such as methaqualone and diphenhydramine (Mandrax) which accounts for 6 per cent, tricyclic antidepressants (Tryptizol, Tofranil) 10 per cent and the benzodiazepines (Mogadon, Librium and Valium) 20 per cent. Salicylate poisoning, frequently encountered in younger people, amounted to 10 per cent and carbon monoxide, often the choice of the elderly, 2 per cent.

Combinations of drugs are taken frequently and alcohol also may be involved. This gives rise to problems in assessment of the severity of poisoning and in treatment; chemical analysis may be rendered more difficult.

Suicide. The methods adopted for deliberate self-destruction vary from country to country and between the sexes. In Britain domestic gas poisoning is still the most common method employed by both sexes. In women the second choice is drugs and the third drowning. In males the second choice is by self injury, such as hanging or strangulation and the third choice poisoning with drugs. In America, where firearms are more readily available, this is the first choice by males but only the second by females. Poisoning by drugs is the first choice of females. In the United States coal-gas has largely been replaced for domestic use by natural gas which is in itself not toxic; this has resulted in a steep decline in the use of gas for suicidal purposes and as a cause of accidental poisoning. Despite this decline the total incidence of poisoning has not fallen. A similar trend is likely to emerge in Britain.

Diagnosis of Acute Poisoning

Information Service. With the increasing frequency of accidental and intentional poisoning it is important to determine whether the substance ingested is noxious. In the United Kingdom and Eire a Poisons Information Service is available to doctors telephoning one of the following numbers:

GOVERNMENT SPONSORED

Belfast: Royal Victoria Hospital. Tel. 0232-30503.
Cardiff: Royal Infirmary. Tel. 0222-33101.
Edinburgh: Royal Infirmary. Tel. 031-229 2477.
Eire: Jervis Street Hospital. Tel. Dublin 45588.
London: Guy's Hospital. Tel. 01-407 7600.

OTHERS

Leeds: General Infirmary. Tel. 0532-32799.
Manchester: Booth Hall Children's Hospital. Tel. 061-740 2254.

Information can be immediately obtained regarding the ingredients of a sul stance; the fatal dose of a poison and the best method of treatment can b discussed with a physician trained in clinical toxicology.

Differential Diagnosis. In Britain acute poisoning is the most common caus of unconsciousness, in the absence of head injury, in a patient between 15 an 50 years. The diagnosis of acute poisoning is usually made on the histor obtained from relatives or friends, from circumstantial evidence, such a finding tablets at the bedside and from a prompt physical examination wit special reference to the degree of unconsciousness and circulatory and respiratory failure. In addition, a decision should be reached as to whether the poiso has been swallowed, inhaled or absorbed from the skin. Few poisons produc diagnostic clinical features, but the smell of coal-gas, the hyperpnoea an sweating of salicylate poisoning, the markedly depressed respiration and pin point pupils of opiate poisoning are helpful diagnostic features on occasions Treatment should not be delayed by spending excessive time in attemptin to identify precisely the poison involved, since there is seldom a specific antidote and the essential immediate treatment of poisoning is dependent on the application of well established basic therapeutic principles. Every hospital. nevertheless, should have some aid to the identification of capsules and tablets which are commonly used in poisoning. For this purpose a coloured diagram or examples of the more common drugs can be mounted on a board. The marking of tablets with code letters and numbers has recently been introduced to a limited extent and has already proved of value in identification. Laboratory analysis of gastric aspirate, blood or urine will confirm the diagnosis. Qualitative and quantitative estimation of carboxyhaemoglobin, salicylate, alcohol, iron and barbiturate (with identification as to whether short, medium or long acting) should be readily available. These results, however, seldom influence management but confirm the diagnosis and may be of value for medico-legal purposes.

General Therapeutic Measures

MAINTENANCE OF RESPIRATION. A clear airway is essential. This can be ensured by removal of dentures, vomitus, foreign bodies and excess mucus: the patient should be turned on his side to prevent the tongue falling backwards and to avoid aspiration of vomitus and mucus. An oropharyngeal or cuffed endotracheal tube may have to be inserted to maintain a free airway. Artificial respiration is required if respiration is depressed, using preferably the method of expired air resuscitation (p. 239). Oxygen should be given through an oronasal mask (p. 331). Prophylactic antibiotics to 'protect' the lungs are not recommended, but any infection which develops should be treated.

REMOVAL OR INACTIVATION OF THE POISON. It cannot be emphasised too strongly that it is very important that the poison must be got rid of as quickly as possible. The first-aid treatment is often the responsibility of the general practitioner in the patient's home while awaiting the arrival of an ambulance. Patients with gassing must be removed to fresh air as quickly as possible. When a liquid or olid poison is in contact with the patient's clothes these must be removed at nce and any poison on the skin must be washed off to prevent absorption. Vhen the poison has been swallowed conscious patients should be given ctivated charcoal prior to transfer to hospital. A decision as to whether emesis nd gastric aspiration and lavage be also undertaken will depend on three actors: (*a*) the substance ingested, (*b*) the state of consciousness of the patient, nd (*c*) the length of time since the poison was ingested.

(*a*) NATURE OF SUBSTANCE INGESTED. The only contraindication to inducing emesis or passing a stomach tube is the knowledge that paraffin oil (kerosene) or other petroleum distillates have been swallowed, as the entry of even a small quantity of these substances into the lungs will lead to a severe pneumonia. Great care must be exercised in passing a stomach tube in corrosive poisoning, in alcoholics, in patients who have had gastric surgery and in the very young and elderly, but the benefits from gastric aspiration and lavage outweigh the potential dangers of perforating the oesophagus or stomach.

(*b*) LEVEL OF CONSCIOUSNESS. The second factor to be considered is the state of consciousness. Fully conscious patients should be made to vomit by putting one's finger into the throat; if initially unsuccessful this can be repeated after giving a tumblerful of tepid water containing a dessertspoonful of common salt. When this is impracticable as in a hysterical, violent patient, apomorphine hydrochloride 5 mg may be given intramuscularly. It is a powerful emetic but unfortunately it can produce hypotension, dangerous collapse and persistent vomiting. These effects can, however, be antagonised by administering 15 mg of nalorphine. Syrup of Ipecac 30 ml, recommended by certain authorities as worthy of a place in every home medicine cupboard, is in practice almost invariably too slow in action and too uncertain to be of value in a potentially seriously poisoned patient.

In a semi-conscious patient emetics are to be avoided in view of the danger of aspiration pneumonia, but gastric aspiration and lavage can be employed provided the cough reflex is still present. Gastric lavage in the deeply unconscious patient without this reflex is a highly dangerous procedure unless the lungs can be protected by the insertion of a cuffed endotracheal tube.

(*c*) TIME SINCE INGESTION. The third factor to be considered is the time which has elapsed since the ingestion of the poison. If four hours have passed since ingestion very little or no recovery of the drug will be achieved by undertaking emesis and gastric lavage; if it is known that the poison was taken less than four hours previously aspiration and lavage must be done. In salicylate poisoning, because of the almost inevitable pylorospasm which prevents the drug from leaving the stomach, it is never too late to undertake these procedures and large amounts of salicylates may be recovered up to 24 hours after ingestion. In the case of tricyclic drugs a worthwhile recovery may be achieved up to twelve hours after ingestion. In other forms of poisoning, provided the two factors already discussed have been considered, gastric aspiration and lavage should be undertaken if less than four hours have elapsed since the drug was consumed.

Technique of Gastric Aspiration and Lavage. With the foot of the bed rais about 0·5 m and the patient lying on his left side a wide-bore Jacques rubb stomach tube, English gauge 30, should be passed. A gag may be necessa to prevent biting on the tube. When the tube has been inserted, its position the stomach is verified by aspiration of stomach contents or by blowing little air through it and auscultating over the abdomen when a bubbling soun will be heard. Aspiration is best achieved by lowering the funnel to which th stomach tube is attached, to a level well below the patient's head. Aspiratio is advisable prior to lavage as initial lavage will drive some of the stomac contents into the duodenum and promote absorption. When no further materia can be aspirated repeated careful lavage with tepid water should be undertaken using the same apparatus and no more than 300 ml for each single washout Lavage should be continued until the returning fluid is clear which may necessitate a total volume of 40 litres. Except in the specific instances shown in Table 14, little is achieved by employing lavage fluid other than water.

On occasions, after lavage, some further impairment of consciousness ma occur; hence, except in iron poisoning, the value of leaving fluid in the stomach may be outweighed by the dangers of subsequent aspiration pneumonia if the patient has had no cuffed endotracheal tube inserted. However, with this possibility in mind and provided that no delay in further treatment is occasioned by the preparation of solutions, the following may be left in the stomach after lavage: 100 ml milk on account of its demulcent properties in corrosive poisoning; the chelating agent, desferrioxamine, in acute iron poisoning (p. 959). It is frequently recommended that on completion of gastric lavage for salicylate poisoning a solution of sodium bicarbonate should be left in the stomach. In the authors' opinion this is not advisable. Although the bicarbonate counteracts the irritation of the gastric mucosa and when absorbed may help to promote excretion of salicylate by rendering the urine alkaline, its presence in the stomach encourages further absorption of salicylate.

If considerable absorption has occurred the patient may be gravely ill, hence measures to enhance elimination of the poison may be required. These can only be carried out in hospital because of the technical skill and special apparatus required; they include (*a*) diuresis (p. 195), (*b*) forced diuresis (p. 958), (*c*) peritoneal dialysis (p. 611), (*d*) haemodialysis (p. 611), (*e*) exchange transfusion (p. 959).

ANTIDOTES. It is widely but erroneously believed that for each toxic substance there is a specific antidote. There are, in fact, no antidotes for the majority of substances producing poisoning. In about 2 per cent of instances, however, certain pharmacological antagonists are of value. An example is nalorphine for opiate poisoning which with others are mentioned in Table 14.

MANAGEMENT OF CIRCULATORY FAILURE. If the patient shows any sign of peripheral circulatory failure the foot of the bed should be raised. Warmth should be applied but sweating must be avoided. For severe shock metaraminol may be given intravenously in a dose of up to 5 mg. Acute circulatory failure may also require treatment by infusion of dextran, plasma or whole blood (p. 252); intravenous hydrocortisone may also be of value.

MANAGEMENT OF HYPOTHERMIA. A rectal thermometer which records low mperatures is required for the accurate assessment of hypothermia. Since it duces the oxygen demands of the tissues, hypothermia is not a deleterious ature unless below 35° C., when it may cause further hypotension, produce udging of the blood and lead to other complications.

In general, active reheating should be avoided, and all that is necessary is to revent further heat loss by nursing in an ambient temperature of 26° C. If he core temperature is less than 32° C., active reheating is indicated and ydrocortisone (100 mg) is given intravenously every 6 hours.

TREATMENT OF CONVULSIONS. Epileptic fits should be controlled with the ntramuscular injection of 15 mg of diazepam and/or 200 mg of sodium phenobarbitone.

Psychiatric Assessment

As most instances of poisoning in adults are deliberate acts of self-poisoning it is very important that all patients, whether suffering from 'accidental' or intentional poisoning, should be assessed by a psychiatrist. Self-poisoning is often an important feature of various psychiatric disorders, and depression in particular. Even if there is no major psychiatric disturbance the techniques of psychiatry are well suited for unravelling the underlying situation. It is greatly to the benefit of the patient if the initial psychiatric interview takes place as soon as possible after the act before the patient and his relatives have time to discuss the event and thereafter present the same rationalised and often false picture.

Barbiturate Poisoning

While barbiturates are most commonly used for intentional poisoning, other hypnotics are also employed, cause similar clinical features and require management based on the same principles.

Clinical Features. In poisoning of moderate to severe degree there may be:

Impaired Consciousness. The degree of impairment will vary and is best expressed by the following classification: Grade 1, response to vocal commands; Grade 2, maximal response to minimal painful stimulation; Grade 3, minimal response to maximal painful stimulation; Grade 4, total unresponsiveness to maximal painful stimulation.

Hypotension. Hypotension is produced mainly by the toxic action of barbiturate on the heart and smooth muscles of the blood vessels. The heart rate is normal or only slightly increased.

Respiratory Depression. Both the rate and depth will be depressed. The clinical assessment of the degree of respiratory depression is very difficult. It can best be measured with Wright's spirometer; a minute volume of expired air of less than 4 litres indicates severe depression necessitating immediate measures to improve ventilation.

Abnormal Reflexes. Diminution or absence of the tendon reflexes varies and

TABLE 14

Some Features and Treatment of Poisoning by less Common Agents

Poison	Signs and Symptoms	Treatment
Amphetamine Group.	Excitement. Flushing. Tremor. Fits. Insomnia. Psychoses. Tachycardia. Hypertension.	1. General measures. 2. Chlorpromazine, 100 mg intramuscularly. If forced diuresis is indicated the urine must be rendered acid.
Corrosives.	Stains and burns of corners of mouth and chin. Burns of fauces. Pain. Shock.	1. General measures. 2. Gastric lavage with care. 3. Neutralise acid or alkali.
Cyanides and Hydrocyanic Acid.	Odour of bitter almonds. Shallow breathing. Pink colour of skin and mucosae. Shock. Widely dilated pupils.	1. General measures. 2. Cobalt edetate (Kelocyanor) 300 mg in 20 ml intravenously over one minute. 3. If no recovery in one further minute, repeat 300 mg cobalt edetate. 4. If ingested, gastric lavage with 25 per cent sodium thiosulphate.
Dinitro-ortho-cresol Weedkillers.	Yellow skin. Severe sweating. Thirst. Fatigue. Tachycardia. Tachypnoea. Raised temperature.	1. Wash skin. 2. Sedatives. 3. Reduce temperature.
Domestic Bleach.	Burning sensation in mouth and fauces. Gastroenteritis.	Gastric lavage with sodium thiosulphate 0·1 per cent if symptoms severe.
Opiates.	Depressed respiration. Pinpoint pupils. Pallor. Vomiting. Coma.	1. If ingested gastric lavage with very dilute pot. permanganate—1 in 10,000. 2. Nalorphine 15 mg intravenously and repeat every 15 minutes till consciousness regained. 3. Keep under observation and repeat nalorphine if necessary.

TABLE 14—*continued*

Poison	Signs and Symptoms	Treatment
Organophosphorous Compounds.	Cold. Sweating. Constricted pupils. Salivation. Twitching. Convulsions. Slow pulse. Bronchospasm. Acute pulmonary oedema. Diarrhoea.	1. Remove contaminated clothes and wash skin. 2. General measures. 3. Atropine 2 mg intravenously and repeat 1 mg intravenously to maintain 'atropinisation'. 4. Pralidoxime (P_2S) 1 g in 5 ml water intravenously. Repeat in 1 hour.
Paracetamol.	Nausea, vomiting, vague upper abdominal pain. Hypotension. Hypothermia, or hyperthermia; the latter, if marked, may be associated with erythema or urticaria. Hypoglycaemia. Bleeding. Renal Failure. Delirium. Acute liver failure may develop a few days after ingestion and carries a high mortality.	1. General measures. 2. Intravenous glucose to correct hypoglycaemia and maintain hydration. 3. Replace diminished clotting factors.
Paraffin and Petroleum Distillates.	Vomiting and diarrhoea. Pallor. Cough and dyspnoea.	1. Do NOT wash out stomach (p. 951). 2. Antibiotics if aspiration has occurred.

is not a good measure of the severity of the poisoning nor is the size of the pupils or the presence or absence of the light reflex.

Oliguria or Anuria. Urinary output may be severely reduced owing to a number of factors such as hypotension, anoxia, a central antidiuretic effect, and a toxic action of barbiturate on the renal tubular cells.

Hypothermia. See page 953.

Skin Lesions. Bullous lesions occur in 6 per cent of cases not only on the pressure bearing areas but also on the hands and feet. The initial lesion is a slightly raised patch of erythema with a sharp outline which may proceed to bullous formation. Bullous lesions are most helpful in differentiating poisoning from other causes of coma.

Raised Blood Level of Barbiturate. The longer acting barbiturates produce higher levels than do the shorter acting preparations, e.g. in a patient severely poisoned with phenobarbitone the level may reach 15 mg per 100 ml whereas with a medium acting preparation such as amylobarbitone, the patient may show features of poisoning of a similar degree when the blood level is only 5 mg per 100 ml. It should be remembered that high blood levels with few features of poisoning may be found in epileptics and others habituated to the drug. This emphasises that assessment of the severity of poisoning must be based on clinical features and not on blood levels. Pre-existing liver disease may exaggerate and prolong the toxic effects of barbiturates.

Additional Features of Poisoning with other Hypnotics. In Mandrax (methaqualone and diphenhydramine) poisoning, hyper-reflexia, papilloedema and acute pulmonary oedema occur with, on occasions, a disturbance of the clotting mechanisms. In Doriden (glutethimide) overdosage sudden periods of apnoea and considerable variation in the conscious level may be prominent.

Complications. The complications can be deduced from study of the above list of clinical features. Briefly they are: (1) acute respiratory depression; (2) hypostatic and aspiration pneumonia; (3) severe shock; (4) anuria; (5) fluid and electrolyte imbalance with acid-base disturbance; (6) withdrawal fits and psychoses on recovery of consciousness.

The following complications are the direct effects of treatment: (*a*) aspiration pneumonia from injudicious gastric lavage; (*b*) pulmonary oedema from overloading of the circulation during forced diuresis; (*c*) the hazards associated with haemodialysis and peritoneal dialysis; (*d*) convulsions, cardiac arrhythmias and psychoses from analeptic drugs which should never be used.

Treatment. This is based on the adoption of basic therapeutic principles to maintain respiration (p. 332), support the circulation (p. 252), correct electrolyte imbalance (p. 186) and prevent further absorption of the drug by removal of poison from the stomach. In poisoning producing a mild or moderate impairment of consciousness sometimes no additional medical treatment is required but under careful nursing supervision the patient should be left to sleep off the effects of the drug. In the severely poisoned patient, treatment in hospital includes assisted respiration (p. 332), measures to combat shock and dehydration (p. 252) and possibly measures for enhanced elimination of barbiturate from the body. These subjects are discussed under general therapeutic measures (p. 950) and in other chapters of this book. There is no specific barbiturate antagonist and bemegride is merely a respiratory stimulant and is no better than nikethamide for this purpose.

Prognosis. As a result of effective treatment the mortality rate for patients suffering from barbiturate poisoning admitted to a well equipped and staffed hospital has fallen from 25 per cent to 1 per cent in the past 20 years.

Benzodiazepine Poisoning

This group of drugs comprising nitrazepam (Mogadon), diazepam (Valium) and chlordiazepoxide (Librium) is now taken in overdosage as frequently as barbiturates. However the effects are very different; the ingestion of as many as 100 tablets of nitrazepam will produce no more than a deep sleep from which the patient can be roused. No hypotensive effects occur and only very rarely is there any depression of respiration. No medical treatment other than supervision is indicated.

Poisoning by Tricyclic Antidepressants

These include amitriptyline (Tryptizol), imipramine (Tofranil) and trimipramine (Surmontil). The effects in overdose include dryness of the mouth, fixed dilated pupils, sinus tachycardia with bizarre arrhythmias, hypotension, marked irritability with hyperreflexia which may lead to convulsions, loss of consciousness, absent bowel sounds and urinary retention. The dangerous effects are those on the heart and to a lesser extent the convulsions. Intensive supportive therapy is required with anti-arrhythmic drugs (p. 233) as indicated. Convulsions will be controlled with diazepam, 15 mg intravenously, together with phenobarbitone 200 mg intramuscularly.

Salicylate Poisoning

The patient is almost always conscious, hence simple questioning regarding consumption of salicylates will usually prevent the condition from being misdiagnosed as diabetic keto-acidosis or a severe infection, especially of the respiratory tract. Salicylates are often taken in compound tablets with codeine and phenacetin but the important acute toxic ingredient is the salicylate.

Clinical Features. A moderately to severely poisoned patient may show some or all of the following:

Roaring in the Ears, Deafness and Blurring of Vision.

Restlessness and Sweating. These result from the stimulant effect of the drug and an increased metabolic rate.

Hyperventilation. The drug also has a direct stimulant effect on the respiratory centre increasing the depth and rate of ventilation, producing a lowering of the $Paco_2$ and a respiratory alkalosis.

Epigastric Pain and Vomiting. The combination of loss of gastric contents, hyperventilation and profuse sweating leads to severe dehydration and a reduced urinary output.

Biochemical Changes. The serum potassium, despite dehydration, will be low as a result of the initial respiratory alkalosis. The latter may be replaced by a metabolic acidosis, especially in children.

Urinary Changes. Proteinuria may occur and renal tubular casts and cells may be found in the urinary deposit. A purple colour will appear on Phenistix testing.

Serum Salicylate. The level will be 50 mg or more per 100 ml.

Complications. Profound disturbances of acid-base equilibrium, especially when associated with impaired consciousness, are to be regarded as a very serious feature and may herald sudden death, but the underlying mechanis is not fully understood.

Despite the tendency for salicylates to cause gastric erosion and hyp prothrombinaemia, haematemesis rarely occurs and blood-stained gastr contents evacuated by lavage are seldom seen.

Although protein and renal tubular cells are often present in the urine durin the acute stage, permanent renal damage has not been recorded.

Treatment. Moderate to severe salicylate poisoning is best treated in an adul by gastric aspiration and lavage (p. 952) which should never be omitte irrespective of the time that has elapsed since the drug was taken.

Salicylate can best be eliminated from the body by forced alkaline diuresis The urine must be rendered alkaline since a rise in urinary pH from 6 to 7· increases the excretion of free salicylate tenfold. For this purpose the followin should be mixed together and given intravenously at a rate of 2 litres hourl for three hours:

Saline (0·9 per cent)	0·5 litre
Dextrose (5 per cent)	1 litre
Sodium bicarbonate (1·26 per cent) .	0·5 litre
Potassium chloride	3 g

If forced alkaline diuresis cannot be undertaken or if a diuresis is not achieved, peritoneal dialysis or haemodialysis will be required.

Prognosis. The mortality from salicylate poisoning is 1 per cent if effective forced diuresis is employed.

Carbon Monoxide Poisoning

Although poisoning by this gas carries by far the highest mortality both in and out of hospital, the incidence of coal gas poisoning is diminishing throughout the world. The amount of carbon monoxide in domestic gas in Britain is being reduced and the danger will be averted by the use of natural gas which is not in itself toxic. Natural gas can however produce carbon monoxide when incomplete combustion occurs through, for example, the burning of natural gas in unsuitable appliances. Natural gas may also be harmful by simply displacing oxygen in a closed space.

The smell of coal gas is usually evident but may be absent if the gas coming from a broken pipe has seeped through a layer of earth. It is unusual to encounter a deeply comatose patient in hospital because victims who reach that stage usually die at the site of poisoning.

Since the carbon monoxide in coal-gas combines so strongly with haemoglobin to form carboxyhaemoglobin, which is two hundred and ten times more stable than oxyhaemoglobin, the clinical features will be those due to varying degrees of hypoxia. These include disorientation or coma, varied arrhythmias, severe hypotension and heart failure. Respiration is usually rapid and deep. The tendon reflexes are increased and the plantar responses may be extensor; the pupils may be dilated. Skin pallor is common but patchy erythema and even bullae may develop.

By itself the percentage saturation of carboxyhaemoglobin is not a reliable ndication of severity nor a good prognostic index. It will be about 30 per ent for moderate poisoning and about 50 per cent for severe poisoning, provided here is no associated anaemia.

Treatment. The basic necessity is to remove the patient immediately from he source of gas and, without any delay, apply respiration if indicated. Oxygen hould be given. Admission to hospital is essential, resuscitative measures being maintained during transportation. In hospital the dangers of hypoxia, especially to the cardiac muscle, must be remembered and the patient should be kept resting quietly for several days until it is certain that the heart has escaped damage. Acute cerebral oedema may be promptly reduced by the rapid infusion of mannitol (p. 837). At the present time the hyperbaric oxygen chamber is of limited value in the treatment of carbon monoxide poisoning because of the time which usually elapses before the patient reaches hospital.

Acute Poisoning in Children

Accidental poisoning in children under 4 years of age is an all too common event. Two-thirds of the enquiries dealt with by the Poisons Information Service are about children who have taken a substance which may be noxious. Analysis of the enquiries has shown that whilst sugar coating and colouring of tablets are frequently attractive, an unpleasant odour or taste does not prevent toddlers from sampling a substance. Domestic bleaches and detergents are amongst the most common substances consumed; fortunately they are relatively innocuous and, apart from symptomatic treatment for the irritant effects on the alimentary tract, require no particular management. Poisoning by drugs can be serious in children, especially when salicylate or iron tablets have been ingested. Most of the clinical features of salicylate poisoning resemble those already described in adults but it should be remembered that children are especially susceptible to the severe acid-base disturbance which occurs in this form of poisoning and which may develop at blood levels of salicylate which are not considered dangerous in adults. Exchange transfusion is a valuable therapeutic procedure in severe salicylate poisoning in little children.

Poisoning with iron salts which formerly carried a high mortality, is now effectively treated with the chelating agent, desferrioxamine, given via the gastric tube, intramuscularly and by intravenous infusion. Speed is essential in starting treatment which may be summarised in dosages appropriate for adults which will require adjustment according to the age of the child:

1. An intramuscular injection of 2 g of desferrioxamine is given immediately.
2. Gastric lavage is performed with appropriate volumes of a solution of desferrioxamine (2 g) in 1 litre of warm water, following which 5 g of desferrioxamine in 100 ml of water or saline is left in the stomach.
3. This is followed by an intravenous infusion of desferrioxamine in saline, dextrose or blood. The amount should not exceed 15 mg/kg body weight/hour up to a maximum of 80 mg/kg in 24 hours.
4. Full supporting therapy for convulsions, shock, acidosis, blood loss and electrolyte disturbance is essential.

Industrial and Agricultural Poisoning

It is sufficient to record that lead (p. 902), cyanide (p. 954), mercury beryllium (p. 409) and cadmium are potential causes of industrial poisoning In agriculture many highly toxic weedkillers, including paraquat and the dinitro ortho-cresol group and the insecticides belonging to the organo-phosphoru compounds have been developed in recent years. They have been responsibl for only a small number of cases of acute poisoning in Britain owing to adequat and effective legislation for controlling their use. In some countries, however they have caused many deaths each spring.

A. A. H. LAWSON.
HENRY MATTHEW.

Further reading:

Matthew, H. & Lawson, A. A. H. (1974). *Treatment of Common Acute Poisonings*, 3rd ed. Edinburgh and London: Churchill Livingstone.

Tropical Diseases and Helminthic Infections

OVER one-half of the world's population live in areas where tropical diseases nd malnutrition still undermine the health of a large proportion of the people. Some diseases are strictly tropical because the vectors, such as the tsetse flies, which convey the trypanosomes causing African sleeping sickness, are limited to the tropics, but many prevail because of poor hygiene. The method of attack on tropical diseases should, therefore, be preventive rather than curative. In the tropics this depends largely on the institution and maintenance of effective sanitation, drainage and a safe water supply. Education of the people in ways of cleanliness is essential to ensure that the available sanitary facilities are properly used. As a first step in underdeveloped areas, health visitors, practical men and women living in the villages, can do much to educate people in simple but effective measures against disease. A little money used on these lines will do far more good than large sums spent on expensive drugs for the treatment of preventable diseases. For example, spraying with insecticides has greatly reduced the incidence of malaria and vaccination campaigns have been successful in preventing smallpox, yellow fever and tetanus neonatorum.

Many of the inhabitants of tropical countries are so weakened by disease and malnutrition that they are unable to produce sufficient food even for their own needs. By controlling tropical illnesses the health of the people will be so greatly benefited that production of food and raw material may reach and even exceed local requirements, the surplus then becoming a source of revenue. With these improved conditions there will inevitably be an increase in the birth rate and a fall in infant mortality. Instead of only 3 out of 10 children surviving to reach adult life 7 or 8 of the 10 may do so. The resulting swelling of the population creates new economic and social problems and in many countries instruction in family planning has become an urgent necessity. The World Health Organization and other public bodies are providing valuable aid to underdeveloped countries by financing projects in medicine, agriculture, engineering and science which must later become an integral part in the overall national effort. The execution of these plans entails great capital outlay as well as the provision of many experts. The maintenance of improved health is dependent on a sound economy and political harmony.

Historical Aspects

The history of many of the tropical diseases goes back to the earliest days. The cardinal signs of malaria were described by Hippocrates. The Romans thought that it was due to bad air rising from the marshes, and by draining them they reduced unwittingly the breeding-places of the mosquitoes and so had less malaria. Effective treatment with cinchona bark was known long before the malaria parasite was first demonstrated by Laveran in 1880. Then in 1897 Ronald Ross, encouraged by Manson's discovery of the transmission of a filaria by mosquitoes, searched for and found oöcysts in the stomach wall anopheline mosquitoes which had previously fed on persons suffering fr malaria. The following year, working in Calcutta with sparrows infected w bird malaria, he found that culicine mosquitoes fed on these sparrows develop similar cysts in the stomach wall; these eventually burst and liberated bod which reached the salivary glands of the mosquito. He next showed that the mosquitoes conveyed the infection to healthy sparrows. From this he deduc that human malaria was conveyed from man to man by infected mosquitoe and this was shortly afterwards demonstrated by Italian workers.

Despite this knowledge of the method of spread of the disease there w little improvement in the malaria situation until the Second World War whe the urgent need to maintain a non-immune population in highly malariou areas stimulated research into methods of personal protection. It was establishe that a daily dose of mepacrine enabled soldiers to serve in highly malariou areas and to remain free from symptoms. Since then antimalarials with fewe side-effects have replaced mepacrine. Except where strains of parasites resistan to the antimalarial in use have emerged, non-immune persons taking the dru remain free from malaria. Perhaps of even greater importance, huge areas, suc as much of India, formerly endemic for malaria, have been virtually free from infection chiefly by the widespread application of insecticides such a dicophane (DDT), sometimes in combination initially with chemoprophylaxis. Such eradication campaigns, usually initiated by WHO, require careful planning and subsequent vigilance to ensure that malaria does not return, as it did in Ceylon in 1968. Concern over the deleterious effects of accumulations of DDT in the soil and agricultural products is leading to the use of other insecticides free from this disadvantage.

Another disease, kala azar, was long considered to be a form of chronic malaria until Leishman in 1903 discovered the causal protozoon in the spleen of a soldier from Calcutta, and in the following year Rogers cultured it and found that it then assumed a flagellate form. Before the discovery of the curative properties of intravenous antimony, kala azar decimated rich populous tracts of Bengal and Assam. It is still a prevalent disease in certain tropical and subtropical countries and is liable also to attack visitors who may develop fever and hepatosplenomegaly after leaving the endemic area.

The use of emetine and other drugs in the treatment of amoebiasis has enormously reduced the incidence of liver abscess, its most important complication, although amoebiasis is still a common disease in many parts of the world.

For centuries epidemics of louse-borne typhus have occurred when people are brought together under poor hygienic conditions and become verminous. By protective vaccination and the use of DDT as a lousicide it is now possible to prevent this disease. The success of chloramphenicol and tetracycline in the treatment of louse-borne, mite-borne and tick-borne typhus has also completely altered the outlook in these diseases. Recovery can now be expected even when treatment has been much delayed. A protective vaccine is also available for Rocky Mountain spotted fever, a variety of tick-borne typhus.

De Lesseps, who built the Suez Canal, was defeated by malaria and yellow fever in his attempt to construct the Panama Canal in 1880. The American ellow Fever Commission in 1901 proved that urban yellow fever was trans-itted by the bite of the mosquito *Aedes aegypti*. Gorgas, by applying this nowledge, eradicated the disease from the Panama area in 1905 by the destruc-on of this vector. Although yellow fever persists in primates and mosquitoes some forest areas, and urban outbreaks still occur, vaccination with 17D ttenuated yellow fever virus now provides a sure protection against the disease.

The havoc wrought by plague is recorded in the Old Testament. The Great Plague of London in 1664-65 killed 70,000 of London's 460,000 inhabitants. Now the disease is largely prevented by antirodent measures and insecticides nd can also be successfully treated with antibiotics.

Cholera, an ancient disease of the Far East, spread from India to reach Britain in 1832 and thence travelled to USA and Canada. Improved sanitation and water supplies caused its disappearance from Europe by 1895. It occurred in East Africa between 1821 and 1870 and affected Gambia in 1869. Subsequently cholera remained endemic in Asia especially affecting pilgrims visiting crowded endemic areas. In 1947 there was a large outbreak in Egypt and since 1961 cholera due to the *Vibrio eltor* has spread widely in the Far East, South-East Asia and in the Middle East and in 1970 occurred also in southern USSR, Ethiopia and Guinea, followed by outbreaks in Nigeria and Kenya with isolated cases elsewhere including Britain.

Trypanosomiasis of man and animals is due to a variety of trypanosomes. African sleeping sickness, its most serious human manifestation, formerly occurred in devastating epidemics. Animal trypanosomiasis in Africa is also of great importance to human health and economy as it reduces the areas where cattle can be kept. These forms of trypanosomiasis are spread by tsetse flies. By studying their habits and applying appropriate control measures and by using potent drugs for human protection and treatment the incidence of the disease has been greatly reduced.

Leprosy was described in ancient Egypt in 1350 B.C., in the time of Rameses II. The establishment of colonies for patients with leprosy in the infectious stage may have helped to limit the spread of the disease. Great progress has been made since 1944 by the introduction of dapsone and other drugs which successfully combat the causative organism. Patients now frequently come for treatment at an early stage before deformities have arisen. BCG vaccination and specific drugs given to children at risk are of some value in prophylaxis. Nevertheless leprosy still affects about 15 million people mainly living in tropical and subtropical countries.

Schistosomiasis is an ancient disease. Early Egyptian medical papyri record that haematuria was common, and calcified ova of *Schistosoma haematobium* have been demonstrated in the kidneys of Egyptian mummies of the twentieth dynasty, 1250 to 1000 B.C. Bilharz in 1851 described the adult worm found in the portal vein of man. The intermediate host was proved by Japanese workers to be a freshwater snail. In 1915 Leiper observed that the development of *S. haematobium* and *S. mansoni* took place in different freshwater snails. He showed that these were two distinct species of parasitic worms. In 1917 Christopherson introduced effective treatment with antimony salts given intravenously. Other drugs have since been developed but new irrigation schemes spread the disease unless control measures are maintained.

Diagnosis

In addition to a careful history and thorough clinical examination, a micr scopic investigation is usually essential for the diagnosis of tropical diseas A wet film of the blood may reveal the actively moving microfilariae whi are larval forms of the filarial worms responsible for causing elephantiasis a other lesions in man. It may also show the trypanosomes of African sleepi sickness though, in the gambiense form, these are found more readily in flu obtained from puncture of an enlarged lymph node. A well-stained blood fil will reveal malaria parasites and the spirochaetes which cause relapsing feve Absence of a leucocytosis in a patient with pyrexia who is, or has recently bee in the tropics will suggest the possibility of malaria, brucellosis or typhoi fever. Leucopenia is profound in kala azar. A leucocytosis may indicate lept spirosis or hepatic amoebiasis. An eosinophilia will suggest a recent intestina helminthic infection, filariasis or schistosomiasis. Microscopic examination o the faeces may reveal *Entamoeba histolytica* or ova of the roundworm, hook worm or other helminth.

Air travel increases the likelihood of tropical diseases being encountere outside the tropics. There are specific remedies for most of these diseases, bu delay in diagnosis and in treatment may have the gravest consequences for the patient. Every medical man should, therefore, have a reasonable knowledge o the more common tropical diseases even though he may not intend to practise in the tropics and should ask patients about visits to the tropics.

Only malaria, amoebic dysentery, the more common helminthic infections and rabies are described here. Shortly after arriving in Britain a person may hear that a dog with which he had recently been in contact has died of rabies; under these circumstances no time must be lost in instituting preventive treatment. The other infections have been chosen because of their frequency in this country. Tables 15 and 16 (pp. 974-977) summarise other important tropical diseases and nutritional disorders are described on pages 111 to 172. For further information the tropical diseases supplement to this book should be consulted. When the diagnosis is in doubt, patients should be referred without delay to a centre specialising in this field.

Malaria

Malaria occurs wherever there are human hosts and a sufficiency of malaria-transmitting anopheline mosquitoes together with conditions of temperature and humidity which permit the complete development of the parasite in the infected mosquito. Malaria may also be transmitted by a blood transfusion from an apparently healthy donor from whom the parasites have not been fully eradicated.

The Parasite. The four recognised species of malaria parasites pathogenic to man are *Plasmodium falciparum*, *P. vivax*, *P. malariae* and *P. ovale*. *P. vivax* and *P. ovale* produce a clinically similar 'tertian' fever, the temperature rising on the first and third days and continuing with this periodicity; *P. malariae* oduces a quartan type of fever with apyrexial intervals of two days; *P. ciparum* causes a more continuous fever, the so-called subtertian fever. When female anopheles feeds on infective human blood, the sexual forms of the rasite reach the mosquito's stomach. The female macrogametocyte is fertilised the male microgametocyte. The resultant fertilised cell penetrates the stomach all of the mosquito and there forms the oöcyst. Within this cyst sporozoites re developed, and in 7 to 20 days, depending on the temperature, these are berated and travel to the salivary glands of the mosquito. When this infected osquito bites man, sporozoites are introduced. These sporozoites soon dis-ppear from the circulating blood and enter the liver cells, where pre-erythrocytic evelopment takes place. After $6\frac{1}{2}$ days from infection with *P. falciparum* and etween $8\frac{1}{2}$ and 11 days with the other species the infected liver cells rupture nd liberate numerous merozoites which then infect the red blood corpuscles. n *P. falciparum* infection all the parasites in the liver mature about the same ime and all are discharged into the circulation, while in the other malarial nfections exoerythrocytic forms persist for months in the liver cells where they cannot be reached by most antimalarial drugs. This accounts for the frequency of relapses in these forms of malaria and the absence of relapses in falciparum infection after stopping drugs which have removed the parasites from the circulating blood. On entering the red cells the young parasite appears as a ring form, and its development thereafter is shown in Plate IV (p. 968). When the schizont is mature, the red cell ruptures and liberates a new generation of merozoites which enter other red blood cells and develop into either asexual or sexual forms. These gametocytes begin to appear about 7 to 10 days after the asexual forms; they cause no symptoms but make the individual harbouring them a reservoir of infection.

Clinical Features. When merozoites in sufficient numbers are liberated from dividing schizonts into the plasma, a febrile reaction is caused in the human host. The interval from the time of biting by the infected mosquito to the onset of detectable fever varies but is often about a week or 10 days for *P. falciparum* infections and somewhat longer for vivax and malariae malaria. Occasionally an apparent primary attack of vivax malaria occurs months after the patient has left the tropics, and suppressive drugs may delay the onset for as long as a year after stopping the drug. In many cases vivax malaria starts with a period of several days of continued fever before the development of classical bouts of fever on alternate days. The attack has three clinical stages: first a cold stage, followed by a hot stage, which ends in a sweating stage. In the cold stage or rigor the patient feels intensely cold and shivers, and frequently his teeth chatter. The temperature is already elevated and rapidly reaches its height, e.g. 40° C. Vomiting is often troublesome and headache severe. After half an hour or so, the hot stage is reached: the patient feels burning hot and may be delirious —vomiting often continues into this stage. After one to six hours, profuse perspiration starts, the temperature drops and the patient becomes comfortable and falls asleep. He will feel reasonably well on the next day, but fever subsequently recurs with a periodicity characteristic for the infecting species. Usually the spleen and, especially in children, the liver become palpable and tender, but the absence of detectable splenic enlargement does not exclude malaria. Herpes simplex, usually round the mouth, is a common accompanim of malaria.

P. falciparum infections, especially primary attacks, are more insidious a dangerous than other forms of malaria. The fever in this variety is prolon and irregular and does not usually rise to quite so high a level as in vivax malariae malaria. Sometimes the patient, although very ill, remains afebr with a heavy *P. falciparum* infection. The cold, hot and sweating stages a seldom found in this form of malaria, but vomiting and severe headaches a common. A severe haemolytic anaemia develops. In uncomplicated cases or the ring stage of the parasites and later the gametocytes are found in the pe pheral blood, whereas in vivax, ovale and malariae malaria all stages of t parasites occur in the circulating blood. A patient with falciparum malari apparently not seriously ill, may suddenly develop complications which rend his condition very grave.

A mixed infection with more than one species of malaria parasite may occu —therefore the demonstration of *P. vivax* does not exclude the possibility o a *P. falciparum* infection.

P. malariae malaria is usually associated with mild symptoms and bouts o fever every fourth day. With this infection parasitaemia may persist for man years without producing any symptoms.

Complications of Falciparum Malaria. These are due to interference with th capillary circulation, destruction of erythrocytes, or toxaemia. The symptom and signs associated with impaired capillary circulation depend on the situatio and extent of the vessels involved. In cerebral malaria the cerebral capillarie are affected causing the rapid onset of coma, hyperpyrexia or mental change and, exceptionally, signs of a focal lesion such as aphasia, hemiplegia or monoplegia. Vomiting, diarrhoea or acute renal failure may result from involvemen of intestinal or renal capillaries.

Blackwater Fever. This is brought about by a rapid intravascular haemolysis and is invariably associated with a chronic falciparum malaria, most commonly in those who have taken antimalarial treatment irregularly. This haemolysis may be quite unexpected and very extensive, destroying many uninfected as well as parasitised red cells. The attack is not infrequently provoked by injudiciously administered quinine or by fatigue. The colour of the urine varies from dark red to almost black, depending on the amount of intravascular haemolysis. Acute renal failure may follow.

Relapses. These are characteristic of vivax, ovale and malariae malaria and are due to persistence of the exoerythrocytic form of the parasite in the liver. Immunity eventually overcomes the infection, and relapses seldom occur longer than two years after the patient has left the malarious area.

Endemic Malaria. The manifestations of malaria in unprotected indigenous residents show considerable variation according to the degree of endemicity and the age of the patient. In areas of hypoendemicity little immunity is acquired, epidemics of malaria are liable to occur and the disease does not differ materially from that in non-immunes. In mesoendemic areas malaria is frequent but only sonal. Repeated infections lead to anaemia, considerable enlargement of een with the danger of its rupture from a minor blow, and chronic ill-health th bouts of fever. The growth and development of children may be retarded d *P. malariae* infections may cause the nephrotic syndrome in them by an munological reaction. Where malarial transmission takes place throughout e year, but with seasonal increases, the zone is termed hyperendemic, and ults show considerable immunity. Although adults will have palpable spleens d occasional parasitaemia, in them malaria causes only occasional short outs of fever. In holoendemic areas malarial transmission is intense throughout e year and adults possess almost complete tolerance for the infection, a con- tion called 'premunity', and enlargement of the spleen in them is uncommon. ross splenomegaly and anaemia due to abnormal immune processes occur, owever, in some adults in these areas. In hyperendemic and in holoendemic reas malaria takes a toll of older infants and young children. The regular taking f antimalarial drugs prevents the manifestations of chronic malaria but impairs he development of immunity. Individuals whose haemoglobin is a combination f sickle-cell and normal haemoglobin or is deficient in G-6-PD (p. 738) are elatively resistant to falciparum malaria.

Malaria in Pregnancy and Childhood. Parasitisation of the placenta frequently causes abortion. The mother may be very ill and have a severe macrocytic anaemia. Impairment of immunity may occur during pregnancy. Indigenous babies in hyperendemic areas have some inherited immunity for the first few months but other infants and young children are very susceptible and in them the onset may be insidious with only gastrointestinal or pulmonary symptoms. The child may become dangerously anaemic or convulsions, coma and death may quickly supervene if adequate treatment is not promptly given.

Diagnosis. If a patient is in a malarious locality or has recently left such an area, malaria should be considered. A history of periodic fever, perhaps associated with an enlarged spleen and anaemia, is very suspicious. Well-stained blood films, thick and thin, should be examined and repeated if necessary. *P. falciparum* parasites may be very scanty. Especially in those who have recently taken ineffective doses of an antimalarial drug parasites may be difficult to find. Where the clinical condition of the patient makes a diagnosis of malaria probable, it may be justifiable to give antimalarial treatment even though parasites have not been demonstrated.

Treatment. GENERAL. The patient should be put to bed and encouraged to drink fluid freely. Aspirin or paracetamol is useful for the relief of headache. During the cold stage hot-water bottles and extra blankets are required. When dehydration is marked and vomiting troublesome, intravenous infusion of saline and glucose may be necessary.

SPECIFIC THERAPY. This should be started as early as possible, especially in falciparum malaria. The drugs of choice are the 4-aminoquinolines, chloroquine or amodiaquine. The usual chloroquine tablets contain 150 mg of the effective chemical base and amodiaquine 150 or 200 mg of the base. A course of treatment consists of 4 tablets followed by 2 tablets in six hours and 2 tab daily for three more days. In a few areas patients have been found infected v a *Plasmodium falciparum* resistant to 4-aminoquinolines; such require treatm by quinine dihydrochloride 600 mg three times daily for 10 days or by a combi tion of sulfoxine 1 g and pyrimethamine 50 mg given in a single dose. N of these drugs, however, ensures that there will be no relapse in vivax, ov and malariae malaria from exoerythrocytic parasites in the liver cells invad the circulating erythrocytes. Proguanil (p. 969) and pyrimethamine are both t slow in action for effective use alone in the treatment of an acute attack malaria in non-immune subjects. Small doses of antimalarials may be adequa to curtail fever in indigenous residents in endemic areas.

TREATMENT OF COMPLICATED *P. falciparum* INFECTIONS. Patients severely ill wi falciparum malaria must be treated as medical emergencies. The immedia intravenous administration of chloroquine or quinine is indicated, the dr being given very slowly to avoid peripheral circulatory failure or acute encephal pathy, taking at least 10 minutes to give the full dose, repeated, if necessar after four to six hours. Ampoules of chloroquine in aqueous solution containi 200 mg in 5 ml are available and 200-300 mg should be given; the dose f quinine dihydrochloride is 500 mg dissolved in at least 10 ml of isotonic salin The dosage of chloroquine for small children must not exceed 5 mg per k body weight, as fatal encephalopathy may occur with larger doses and intravenous or even intramuscular quinine may be safer. Severely ill patients usuall require intravenous saline, and the antimalarial drug may be injected into th delivery tube of the infusion. The results of prompt treatment are very gratifying Dexamethazone, in doses of 4-10 mg intravenously, repeated after four to si hours has been employed successfully in a number of cases. Blood transfusion may be required to combat severe anaemia. In less fulminating cases, chloroquine may be given intramuscularly with excellent results. If, in the treatment of the comatose patient, return to consciousness is delayed, lumbar puncture is indicated to exclude co-existing forms of meningitis. Oral therapy should replace parenteral treatment as soon as the patient's condition allows. A liberal supply of fluid should be given by mouth as soon as the patient can take and retain this, and a normal diet should be provided as soon as it is acceptable to the patient.

Treatment of Blackwater Fever. This depends on the amount of blood which has been destroyed. When there has been severe haemolysis leading to a marked degree of anaemia, circulatory and renal failure may ensue and blood transfusion is urgently needed to replace the destroyed red blood cells and to restore the circulation. Corticosteroids are of value in preventing further haemolysis. It is very important that physical and mental rest should be secured; good nursing and sedatives are of great value. Sufficient fluid must be given by mouth, or intravenously if necessary, to ensure a urinary output of more than a litre in 24 hours. Careful records of fluid intake and output must be kept and appropriate treatment should be instituted if features of acute renal failure develop (p. 609).

RADICAL CURE OF MALARIA DUE TO *P. vivax*, *P. malariae* and *P. ovale*. While relapses can usually be prevented by taking one of the antimalarial drugs in

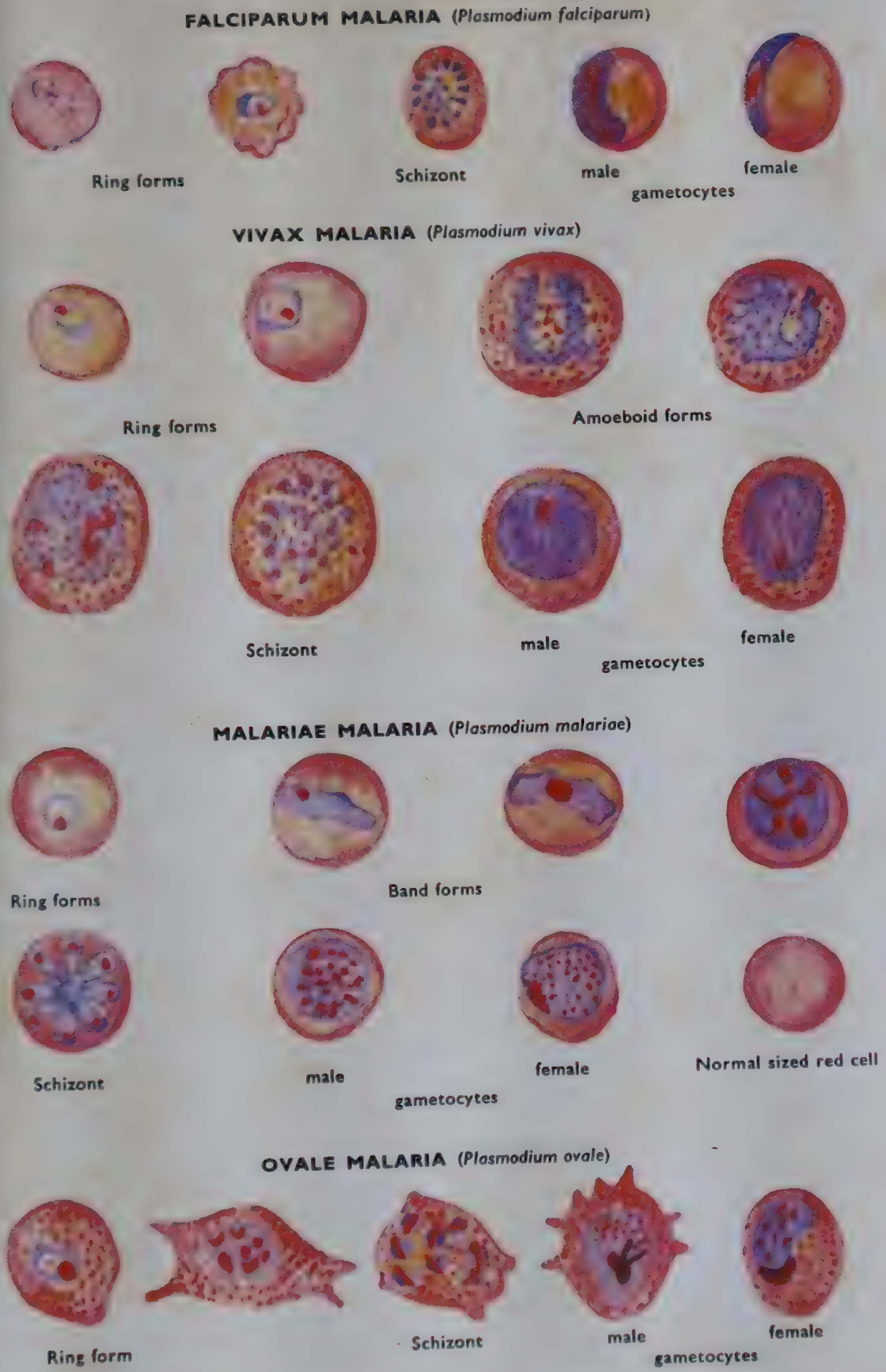


PLATE IV—MALARIA PARASITES

(Modified from 'Manson's Tropical Diseases'. London: Cassell.
Drawings by Sir Philip Manson-Bahr.)

Facing page 968]

suppressive doses over a period of months, radical cure can be ensured only by a course of one of the 8-aminoquinolines, which destroy these parasites in their exoerythrocytic phase in the liver; chloroquine or amodiaquine for four days should immediately precede the course. Primaquine is probably the least toxic of the 8-aminoquinolines; each tablet contains 7·5 mg of base; a course of two or three such tablets taken daily for 14 days produces a high percentage of cures. The patient must, however, be under medical supervision for this period as haemolysis may develop. This is relatively frequent in Negroes, affecting those whose erythrocytes are deficient in glucose-6-phosphate dehydrogenase. Cyanosis due to the formation of methaemoglobin in the red cells is frequent but not dangerous. Relapses after leaving endemic areas can be prevented by an alternative regime of 10 weekly doses of chloroquine 300 mg base with primaquine 45 mg base (six tablets). Mild diarrhoea on the days of treatment is usually the only side-effect.

Causal Prophylaxis and Suppression. So far no drug is known which will destroy the sporozoites injected by the mosquito. Clinical attacks of malaria can, however, be prevented by drugs which attack the pre-erythrocytic form ('causal prophylaxis'), or by drugs which act on the parasite after it has entered the erythrocyte ('suppression'). Both proguanil and pyrimethamine destroy the pre-erythrocytic stage of *P. falciparum*; they also act on the asexual erythrocytic forms of all species of human malaria parasites. Consequently they give reliable protection against clinical attacks of malaria if started on entering a malarious region. These two drugs also prevent further development of the falciparum gametocytes in the mosquito. The adult dose of pyrimethamine is one tablet (25 mg) once a week; for a child up to 6 years $\frac{1}{4}$ tablet (6·25 mg) and from 6 to 12 years $\frac{1}{2}$ tablet (12·5 mg) weekly is adequate. It has an attractive flavour, and some children who have obtained access to the drug have died from an overdose. The suppressive dose of proguanil for adults is 1 or 2 tablets (each containing 100 mg) daily; children aged 1 to 5 years require $\frac{1}{2}$ tablet and under 1 year $\frac{1}{4}$ tablet. Proguanil is a valuable drug for preventing clinical attacks of malaria as it is almost free from side-effects. In addition, since it is taken daily, the routine is unlikely to be forgotten.

Local strains of *P. falciparum* resistant to these two drugs are occasionally encountered; the higher dose of proguanil, namely 2 tablets, can then with advantage be employed, or chloroquine prophylaxis can be substituted. Although chloroquine and amodiaquine are usually effective as suppressants, in some countries where they have been widely used for this purpose strains of *P. falciparum* resistant to these drugs have emerged and constitute a serious hazard.

The adult dose of 4-aminoquinolines is 2 tablets once a week. Children aged 6 to 12 years require 1 tablet and under 6 years $\frac{1}{2}$ tablet. A syrup is also available. Alternatively half doses can be given twice weekly. Occasional toxic side-effects include slight visual disturbance. This makes chloroquine unsuitable for aeroplane pilots. Dapsone 25 mg daily is sometimes used where chloroquine resistance is known to be prevalent. Various combinations of antimalarials are also available.

Prophylactic drugs are ineffective unless taken in the required dose with the

utmost regularity. These drugs should be begun on the day of arrival ir
malarious area and to ensure eradication of *P. falciparum* infection sho
be continued for four weeks after departure. For radical cure of the other for
of malaria see page 968.

Personal Protection against Malaria. Control of anopheline mosquit
especially by the spraying of houses with an insecticide such as DDT h
greatly reduced or abolished the risk of malaria in many areas. Ho
ever, unless eradication is complete, all visitors and non-immune residen
should take regular prophylactic or suppressive drugs as detailed above. Sleepi
at night under a mosquito net or in a wire-screened and sprayed house, w
give freedom from the nuisance of those mosquitoes which bite only in t
dark and may also reduce the likelihood of acquiring some mosquito-bor
viral infections. The use of protective clothing and mosquito boots is becomin
archaic.

Amoebic Dysentery

Amoebic dysentery is typically a subacute or chronic afebrile disease, thu
differing from bacillary dysentery (p. 74) which is an acute disease with
sudden onset often associated with pyrexia. Symptoms of amoebic dysenter
may not appear for months or even years after the infection has been acquired

The *Entamoeba histolytica*, which is responsible for the disease, is found in two phases: a vegetative form, 'trophozoite', actively motile and more easily recognised under the microscope in a fresh warm specimen of faecal blood and mucus, and a resting cystic phase. These cysts are found only in the lumen of the bowel and in the faeces. The vegetative forms invade the mucous membrane of the large intestine. The lesions are usually maximal in the caecum. They may, however, be found as far down as the anal canal. Tiny elevations are produced in the mucosa. These soon break down, producing flask-shaped ulcers varying greatly in size and surrounded by healthy mucosa. Amoebae may find their way into a vein and be carried to the liver where they multiply and cause hepatocellular necrosis ('amoebic abscess'). The liquid contents at first have a characteristic pinkish colour which later may change to chocolate brown and finally to yellow or green. Amoebic ulcers only rarely penetrate through the muscular coat of the colon. A large vessel may sometimes be eroded, and severe intestinal haemorrhage may result. A localised granuloma, 'amoeboma', presenting as a palpable local thickening of the bowel wall and causing a filling defect on radiography, is a rare complication. It responds well to anti-amoebic treatment; it is therefore important that it should not be mistaken for a carcinoma.

Cysts of *Entamoeba histolytica* may continue to be passed in the faeces when the disease is inactive. These, not the vegetative forms, on being ingested are responsible for the spread of the disease.

Clinical Course. Amoebic dysentery usually runs a chronic course with grumbling pains in the abdomen and two or more rather loose stools a day.

symptoms sometimes resemble those of a duodenal ulcer. Periods of rrhoea alternating with constipation are a frequent feature. Mucus is usually sed, sometimes with streaks of blood, and the motions often have a very nsive odour. On palpation of the abdomen there may be tenderness along line of the colon, usually more marked over the caecum and pelvic colon. e right iliac pain may simulate acute appendicitis, and if an operation is formed the amoebae may cause ulceration of the wound and surrounding ue. Perforation, when it occurs, is usually in the region of the caecum. rticularly in the aged, in the puerperium and with superadded pyogenic ection of the ulcers there may be more acute bowel symptoms, with very quent motions and the passage of considerable quantities of blood and mucus, us simulating bacillary dysentery. Bacillary and amoebic dysentery may occur gether, the bacillary infection probably lighting up latent amoebiasis. Macrohages seen microscopically in the stool of patients with bacillary dysentery e sometimes mistaken for amoebae.

Hepatic amoebiasis is a common complication of the bowel infection, and he possibility of this condition must always be remembered in anyone who as lived in the tropics or subtropics. Early symptoms may be local discomfort nly and malaise; later a swinging temperature, sweating and an enlarged tender ver are characteristic, but symptoms may remain vague and signs minimal. In articular, the less common abscess in the left lobe may not be diagnosed. There s usually some increase in the total leucocytes and a raised diaphragm with diminished movement on the right side may be demonstrated radiographically. When hepatic amoebiasis is diagnosed early, before appreciable abscess formation, the response to emetine, metronidazole or chloroquine is very rapid. Delay in recognition may, however, allow a large abscess to form, making the prognosis serious unless adequate treatment is promptly instituted. An untreated liver abscess may invade neighbouring structures or organs, most frequently the lung from where its contents may be coughed up. Rupture into the peritoneal cavity or pericardial sac is usually fatal unless promptly treated surgically.

Diagnosis. The signs and symptoms of amoebic dysentery are often vague. A careful naked-eye examination of a freshly passed motion should be made. If mucus is found, a small piece should be selected and examined at once under the microscope. It should be kept at about body temperature with some heating device so that the *E. histolytica* may retain its motility. Such active amoebae are readily recognised; they are up to 30 microns in diameter or even arger, with a clear ectoplasm and a granular endoplasm, and usually contain red blood cells. Pseudopodia containing clear ectoplasm are protruded and etracted. Movements cease very soon if conditions are not favourable. Sigmoidoscopy may reveal typical ulcers. A scraping from one of these should be examined for *E. histolytica*. Ulcers may, however, be present in the bowel only above the reach of the sigmoidoscope and so escape detection. In chronic amoebiasis a number of stools may need to be examined before cysts are found. Serological tests are now available to support the diagnosis of hepatic amoebiasis. The localisation of abscesses can be made by radio-isotope scanning (p. 538). The fluid from an amoebic abscess of the liver has a characteristic appearance see above) but only rarely contains free amoebae.

Treatment. Emetine has a specific action in controlling the symptom active intestinal amoebiasis. Three to five days' treatment with emetine hy chloride, 60 mg daily, given subcutaneously, relieves the acute symptoms to effect a radical cure this must be followed by an oral amoebicide. Eme bismuth iodide (EBI) is effective but tedious in administration and is now lar replaced by diloxanide furoate 500 mg three times daily for 10 days or me nidazole 800 mg three times daily for five days. Four weeks after the cou the patient should report for test of cure.

Early hepatic amoebiasis responds quickly to treatment by parent emetine, oral chloroquine or metronidazole, a therapeutic response confirm the diagnosis. A standard course of treatment consists of subcutaneous injecti of emetine hydrochloride 60 mg daily for four days, followed by chloroqui 300 mg base, twice daily for two days followed by half this dose for 14 da After treating the hepatic infection eradication of amoebae from the bow is required (see above). In areas of high endemicity very satisfactory resu have been obtained, even after recognisable abscesses have formed, by mass doses (2·4 g) of metronidazole on two successive days and subsequent addition oral amoebicides may not be necessary. If the liver contains a sizeable absce as indicated by a persistent local swelling or continued fever, aspiration, repeat if necessary, or surgical drainage is required in addition to the chemotherap If culture of the 'pus' indicates that there is secondary bacterial infectio treatment will be required with an appropriate antibiotic.

Prophylaxis. Personal precautions against contracting amoebiasis in th tropics and subtropics consist of not eating fresh uncooked vegetables o drinking unboiled water.

Rabies

Rabies is due to a virus which infects a variety of animals and is endemic i many countries. It is spread to man by bites or the licking of an abrasion o mucous membrane, especially by dogs, cats, jackals, or vampire bats. The lengt of the incubation period depends chiefly on the site and severity of the bites. In man it is usually between 30 and 70 days, but it may be as short as 10 days or extend to many months. The maintenance of strict quarantine of imported dogs, cats and other animals for *at least* six months is necessary if rabies is not again to become endemic in Britain.

Clinical Features. At the onset there may be insidious fever or paraesthesia at the site of the bite. Shortly afterwards spasm of the muscles of deglutition appears and irritability progresses until the slightest stimulus, such as the sound, sight or even mention of water, activates spasm of these muscles; hence the alternative name, hydrophobia. The respiratory muscles and others are also affected; delusions and hallucinations develop, with lucid intervals in which the patient is acutely anxious. Paralysis ensues and the patient almost invariably dies within a week of the onset of symptoms. In some the disease takes the form of an ascending myelitis without other symptoms.

reatment and Prevention. Modern methods of maintaining the patient with iratory paralysis may assist recovery from developed rabies, but usually y palliative treatment is possible once symptoms have appeared. Adequate atment early in the *incubation period* will prevent this calamity, as was shown Pasteur in 1885. If possible an animal suspected of having rabies should be killed; it should be kept in isolation under restraint. If it does not die hin 10 days it was not infective for rabies at the time of biting. If it dies, monstration of Negri bodies in the brain or a positive immunofluorescence t confirms the diagnosis. If the victim has been severely bitten a single dose 5,000 units of hyperimmune serum should be given intramuscularly and, if ssible, 5,000 units infiltrated around the wound. In addition, in all probable definite cases, after cleansing the wound, a course of vaccine should be given ee below). In very doubtful cases, especially with only a superficial bite on e leg, the giving of vaccine may be deferred until the dog has died, as the cubation period is over a month after such a bite. If a person is bitten severely r on the face, the incubation period is shorter and treatment must be given t once. Sometimes, especially after inadequate doses of vaccine, the incubation eriod may be prolonged for many months.

The Semple-type vaccine, which has to be preserved in a refrigerator, is given y deep subcutaneous injection, usually in the anterior abdominal wall. This ite is chosen because 2-10 ml have to be administered daily for from 7 to 14 days and these frequent doses can be conveniently spaced here. The dose varies with the age, the severity of the bite and the time of starting the vaccine. Directions accompany the vaccine which should be kept available in administrative centres.

Rarely, serious and even fatal neuroparalytic disorders have resulted from the vaccine, due to sensitivity to its content of animal neural tissue but this risk must be taken if there is reason to believe that the animal was rabid. A vaccine grown in duck embryo is largely free from danger but probably less efficient. Two doses are given, on the 10th and 20th days, after completing the course of Semple vaccine. Duck embryo vaccine may be used alone for minor exposure or licks where risk of infection is low, or for an individual who has been given a Semple vaccine on a previous occasion. Local allergic reactions are reduced by the use of antihistamines, and corticosteroids may ameliorate the neuropathic sequelae.

Vaccine treatment should be stopped immediately if the suspected animal survives for 10 days, as this virtually proves it did not have rabies.

HELMINTHIC INFECTIONS

Helminths or worms which parasitise man belong to three zoological classes: the trematodes or flukes, the cestodes or tapeworms and the nematodes or roundworms. They cause much morbidity in the tropics.

The trematodes of importance include *Clonorchis sinensis*, *Paragonimus westermani* and the schistosomes; among nematodes, hookworms and filaria are scourges (pp. 976-977). These are described in detail in *Tropical Diseases*, the supplement to this book.

TABLE 15

TROPICAL DISEASES

This Table sets out the salient features of the more important tropical diseases not detailed elsewhere in this book. For further information see *Tropical Diseases*, the supplement to this book.

DISEASE	CAUSATIVE ORGANISM	METHOD OF SPREAD	MAIN SYMPTOMS AND SIGNS	TREATMENT
African Trypanosomiasis (Sleeping Sickness).	*Trypanosoma gambiense.* *T. rhodesiense.*	Tsetse flies.	Fever, lymphadenopathy, circinate rashes, finally paralysis and coma.	Suramin, pentamidine, melarsoprol, melarsonyl potassium.
American Trypanosomiasis (Chagas' Disease).	*Trypanosoma cruzi.*	Reduviid (winged) bugs, e.g. *Triatoma infestans.*	Acute. Cutaneous or ocular lesion, fever, lymphadenopathy, myocarditis, encephalitis. Chronic. Cardiomyopathy, heart block; achalasia of cardia; megacolon.	Ineffective. Arsenobenzyl sulphate or primaquine with tetracycline used.
Visceral Leishmaniasis (Kala azar).	*Leishmania donovani.*	Sandflies. (In Mediterranean, dogs are reservoir hosts.)	Prolonged fever, hepatosplenomegaly, lympadenopathy, granulocytopenia.	Pentavalent antimony or pentamidine.
Plague.	*Yersinia pestis.*	Fleas from rats dying of plague. In pneumonic plague, aerosols from man.	1. *Bubonic.* High fever, painful swollen lymphatic glandular mass regional to bite (bubo). 2. *Septicaemic.* High fever, leucocytosis, no bubo. 3. *Pneumonic.* Virulent pneumonitis.	Streptomycin or tetracycline in large doses.
Cholera.	*Vibrio cholerae.* *V. eltor.*	From vomit or faeces of patient or convalescent.	Violent diarrhoea. Vomiting. Rice water stools. Rapid dehydration. Cramps. Hypotension. Anuria.	Intensive intravenous replacement of water and electrolyte losses.
Leprosy.	*Mycobacterium leprae.*	Close contact with lepromatous patient, relative or children's nurse. Organism in nasal mucus.	1. *Tuberculoid.* Asymmetrical hypopigmented anaesthetic patches; thickened nerves; mutilating complications of peripheral neuritis. *M. leprae* scanty or absent. 2. *Lepromatous.* Initial faint macules, then nodules on ears, face and elsewhere. Many *M. leprae* in skin and nasal mucosa	Good food, exercise. Dapsone for years. Thiambutosine is an initial alternative. Clofazimine for reactions. Tuberculoid form indicates a good resist-

TABLE 15—*continued*

Typhus Fevers: 1. Epidemic typhus.	1. *Rickettsia prowazeki.*	1. Faeces of body lice from infected man.	1. Prolonged high fever, severe toxaemia, macular rash.	Tetracycline.
2. Scrub Typhus.	2. *R. tsutsugamushi.*	2. Larval mites from infected rodent.	2. Fever often with eschar at site of bite, and a rash, pneumonitis.	Tetracycline.
3. Tick typhus.	3. *R. conori.*	3. Ticks from dogs, rodents or marsupials.	3. Fever, varying toxaemia, eschar, lymphadenopathy and rash.	Tetracycline.
Many other varieties due also to rickettsiae.				
Yaws.	*Treponema pertenue.*	Non-venereal spread from early lesions through the abraded skin of children.	Early papillomatous proliferative lesions, swelling of bones. Late destructive lesions resembling tertiary syphilis. No visceral or neurological complications. Never congenital.	Long-acting penicillin in a single dose, e.g. PAM (procaine penicillin in 2% aluminium monostearate) 1·2 mega units.
Relapsing Fevers: 1. Louse-borne.	1. *Borrelia recurrentis.*	1. Body lice from man to man.	1. Fever, lasting 5 days, with 1 or 2 relapses after short intervals. Jaundice. Epidemic.	Tetracycline.
2. Tick-borne.	2. *Bor. duttoni.*	2. Infected soft ticks (e.g. in mud huts).	2. As above but repeated relapses, neuropathies as sequelae. Endemic.	Tetracycline.
Yellow Fever.	Arbovirus.	Aedes mosquitoes infected from man (or monkey in jungle yellow fever).	Fever, jaundice, leucopenia, bradycardia, increasing proteinuria. Black vomit. High mortality. Mild cases also occur.	Symptomatic. Vaccination with 17D virus protects for 10 years.
Dengue.	Arbovirus.	Aedes mosquitoes.	Fever, pains in bones, rash.	Analgesics.
Sandfly Fever.	Arbovirus.	Sandflies.	Resembles dengue without a rash.	Analgesics.

TABLE 16

COMMON TROPICAL HELMINTHS

NAME OF HELMINTH	INTERMEDIATE HOSTS	METHOD OF ACQUISITION, MAIN SYMPTOMS AND SIGNS	LABORATORY DIAGNOSIS	TREATMENT
Schistosoma spp.	Freshwater snails.	Acquired by wading in infected water.		
1. *S. haematobium.*	1. *Bulinus spp.*	1. Haematuria, ulceration and papilloma of bladder. Complications, obstruction of ureters, pyonephrosis, carcinoma of bladder, cor pulmonale.	1. Ovum with terminal spine, in urine, stool or rectal mucosa.	For all three species sodium antimonyl tartrate intravenously, stibocaptate or hycanthone intramuscularly are used. For *S. haematobium* orally lucanthone or niridazole if no cirrhosis.
2. *S. mansoni.*	2. *Biomphalaria spp.*	2. Preliminary fever, urticaria and eosinophilia, subsequent mild dysentery. Complications: rectal polypi, fibrosis of liver, splenomegaly.	2. Ovum with lateral spine, in stool or rectal mucosa.	
3. *S. japonicum* (adults, also in mice, dogs, sheep, etc.).	3. *Oncomelania spp.*	3. Clinical features same as 2. Also cerebral granuloma, epilepsy.	3. Ovum with small knob, in stool.	
Hookworms: 1. *Ancylostoma duodenale.* 2. *Necator americanus.*	None.	Acquired by walking barefoot on infected soil. Epigastric pain. Complication: severe anaemia.	Ova in stools.	Tetrachloroethylene or bephenium hydroxynaphthoate.
Strongyloides stercoralis.	None.	Acquired in same manner as hookworms. Minimal intestinal symptoms. Erythematous linear cutaneous eruptions (larva currens).	Motile larvae in stool.	Thiabendazole.

TABLE 16—*continued*

Filariidae: 1. *Wuchereria bancrofti.* *Brugia malayi.* 2. *Loa loa.* 3. *Onchocerca volvulus.*	1. Mosquitoes, esp. *Culex fatigans.* Esp. *Mansonioides spp.* 2. *Chrysops spp.* 3. *Simulium spp.*	1. Mosquito-borne. Recurrent lymphangitis, with fever and eosinophilia. Complications: hydrocele, elephantiasis, chyluria. 2. Bites of chrysops flies. Calabar swellings. Worm may cross eye. 3. Bites of simulium flies. Chronic irritating erythematous maculo-papular rash. Subcutaneous nodules containing adult worms. Complications: Corneal opacities, 'African river blindness'.	1. Microfilariae in blood at night. 2. Microfilariae in blood at midday. 3. Microfilariae in skin snips. A group complement fixation test for 1, 2 and 3.	1. Diethylcarbamazine. 2. Diethylcarbamazine. 3. Diethylcarbamazine, antihistamines, nodulectomy. Suramin for persisting infections.
Dracunculus medinensis (Guinea worm).	*Cyclops* (Water flea).	Swallowing cyclops in well water. Urticaria; later vesicle through which adult female extrudes and discharges fluid containing larvae. Complications: Pyogenic infection of track after death of worm.	Detection of larvae in opalescent exudate.	Slow extraction of adult under sterile conditions. Niridazole aids extraction.
Clonorchis sinensis.	1. Snails. 2. Cyprinoid fish.	Eating uncooked fish. Often symptomless. Cholangitis.	Ova in stool.	Hexachloroparaxylol.
Paragonimus westermani.	1. Snails. 2. Crabs and crayfish.	Eating uncooked crustacea. Fever, cough, 'endemic haemoptysis'. Epilepsy.	Ova in sputum or stool.	Bithionol.

The cestodes, *Taenia saginata* and the larval stage of *Echinococcus granulos* (hydatid cysts) are occasionally acquired in Britain, while a patient with cys cercosis from *Taenia solium* may present as a neurological problem (p. 98 *Diphyllobothrium latum* (the fish tapeworm) is a rare cause of megaloblast anaemia (p. 728).

The only prevalent parasitic helminth in Britain is the nematode *Enterobi vermicularis* (threadworm). *Ascaris lumbricoides* (roundworm), *Toxocara can* *Trichuris trichiura* (whipworm) and *Trichinella spiralis* are the other nematod described below as they also may be acquired in Britain. People having com from the tropics may harbour for years these or other helminths acquire abroad.

Nematodes

(Roundworms)

ENTEROBIUS VERMICULARIS (THREADWORM)

This helminth is common throughout the world, including Britain. It affect children especially. The sexes are separate, the male being 2-5 mm long and th female 8-13 mm (Fig. 98). After the ovum is swallowed, development take place in the small intestine, but the adult worm is found chiefly in the large gut The gravid female worm lays fully developed ova around the anal orifice, and her movements in this region are responsible for intense itching, especially at night. The ova are often carried to the mouth on the fingers of the child and so re-infection takes place. In female patients the genitalia may be invaded. The adult worms may be seen moving on the buttocks or in the stool. Ova are detected by applying the adhesive surface of cellophane tape to the perianal skin in the morning. This is then examined on a glass slide under the microscope.

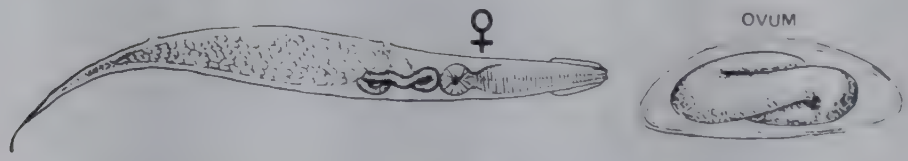


FIG. 98

Enterobius vermicularis

Treatment. Prevention of re-infection is most important. Nails should be kept short, biting of nails forbidden and the hands washed carefully, especially before meals. Piperazine salts are effective remedies. A convenient form is piperazine phosphate administered with senna. The adult dose is 10 g containing 4 g of piperazine phosphate; children under six years are given 5-7·5 g. The drug is given in a single dose but should be repeated if the infection persists. An alternative single dose treatment is viprynium embonate, 5 mg base/kg body weight. Success is more likely to be achieved if the whole family is treated simultaneously, particularly as symptomless infections may be present in adults.

ASCARIS LUMBRICOIDES (ROUNDWORM)

This is a large, pale yellow worm 20-35 cm long, something like an earth-rm, but not segmented. The sexes are separate and the ovum is easily recog-sed under the 2/3 inch lens (Fig. 99).

Man is infected by ova containing developed embryos gaining access to the outh via contaminated fingers or food. The larvae escape from the ova in e duodenum and find their way to the lungs where they develop further. fter invading the alveoli they then ascend the bronchi and trachea and are wallowed, thus entering the intestine where they reach maturity. In heavy infections, such as occur in the tropics, migration of many larvae through the lung may cause a helminthic pneumonitis, with cough, haemoptyses, urticaria and eosinophilia (Löffler's syndrome, p. 381). Adult worms live in the lumen of the small intestine. Symptoms may be absent or consist of nausea, colicky abdominal pain and irregular motions. Sometimes a worm is vomited or passed *per rectum*. In children with severe infections a tangled mass of worms may cause intestinal obstruction. Other complications due to migration of adult worms include blockage of the bile or pancreatic duct and obstruction of the appendix. The diagnosis is made by finding ova in the faeces or by observing an adult worm. A solely male infection is usually revealed only after the giving of an anthelmintic to a patient with an unexplained eosinophilia. Occasionally the worms are demonstrated by radiography.

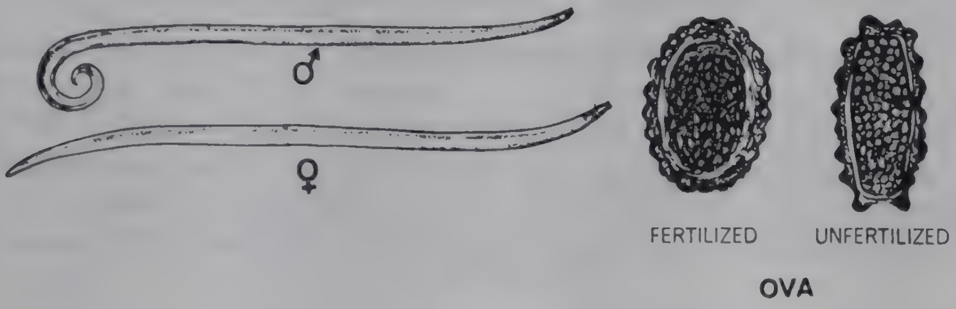


FIG. 99
Ascaris lumbricoides

Treatment. Piperazine salts are easily administered and effective and should be given as recommended for threadworms (p. 978). The worms may not be passed until several days later.

TOXOCARA CANIS

This is a common intestinal ascarid of dogs. The eggs are passed in the animal's faeces. Children who are in close contact with infected dogs are particularly liable to ingest ova of *Toxocara canis*. Larvae, liberated in the stomach, then migrate through the body and may cause allergic phenomena such as asthma, eosinophilia and also splenomegaly. The worms do not usually mature in the human host although they may do so and reach the intestinal lumen. Occasionally a granuloma develops around a dead larva in the and causes an obstruction to vision, resembling a neoplasm.

A skin test using an antigen derived from *T. canis* is employed for diagno There is evidence to suggest that larvae of *T. canis* may be an occasional cau of epilepsy and might convey the virus of poliomyelitis from the intestine the nervous system. The larval worms can be killed by diethylcarbamazi (9-12 mg/kg body weight daily for three weeks) and the adult worms expell by giving piperazine salts as recommended for threadworms (p. 978). Granul mata may require surgical treatment.

TRICHURIS TRICHIURA (WHIPWORM)

Under unhygienic conditions infections with whipworm are common an they are occasionally acquired in rural districts in Britain. Man is the onl host. The ova are passed in stools and infection takes place by the ingestio of earth or food contaminated with ova which have become infective afte lying for three weeks or more in moist soil. The adult worm is 3-5 cm lon and has a coiled anterior end resembling a whip (Fig. 100). Whipworms inhab chiefly the caecum but occasionally also the lower ileum, appendix and colon. There are usually no symptoms, but intense infections in children may cause persistent diarrhoea. The diagnosis is readily made by examining the stools under the low power of the microscope, when the ova are seen. Treatment is by oral thiabendazole in doses of 50 mg/kg body weight daily, in two divided doses for two days.

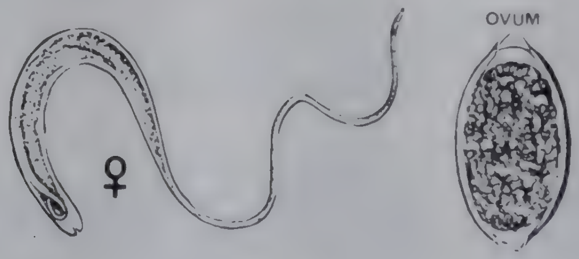


FIG. 100
Trichuris trichiura

TRICHINELLA SPIRALIS

This parasite of rats and pigs is transmitted to man by eating partially cooked infected pork, usually as sausage or ham. Symptoms result from invasion of the body by larvae produced by the adult female worm in the small intestine and from their encystment in striated muscles.

The clinical course of trichinosis depends largely on the number of larvae. If there are only a few worms present there may be no symptoms but many worms may cause nausea and diarrhoea 24 to 48 hours after the infected meal. Soon, however, these symptoms are overshadowed by those associated with larval invasion, namely pyrexia, rapid pulse, and oedema of the face, eyelids and conjunctivae. Invasion of the diaphragm may lead to pain, cough and noea; involvement of the muscles of the limbs, chest and mouth causes ness, pain and tenderness in the affected muscle groups. Pyrexia may reach C. with daily remissions. Larval migration may cause acute myocarditis encephalitis. A leucocytosis with an eosinophilia is usually found after the ond week. An intense infection may prove fatal, but in those who survive nplete recovery is the rule.

Diagnosis. This may be difficult but the disease may be suspected from the nical picture. It is not uncommon for a group of persons who have eaten ected pork from a common source to develop symptoms about the same ne. When suspected, biopsy from the deltoid or gastrocnemius may reveal cysted larvae. A positive biopsy result can be expected from the fourth week ter the onset of symptoms. Precipitin and intradermal tests are also helpful.

Treatment. If diagnosed very early anthelmintics and purgation may remove me of the adult female worms from the gut. Corticosteroids are of considerble value in controlling urgent symptoms. Thiabendazole, 50 mg/kg body eight, on two successive days has been used successfully to relieve persistent ain in muscles. It is believed to act as a larvicide.

Prevention. Pigsties should be kept free from rats. Efficient food inspection r thorough cooking of pork and sausages prevents the disease.

Cestodes

(Tapeworms)

Cestodes are ribbon-shaped worms which inhabit the human intestinal tract. They have no alimentary system and absorb nutrients through the surface. The anterior end, or scolex, is provided with suckers for attachment to the host. From the scolex arises a series of progressively developing segments, the proglottides, which when shed may continue to show active movements for some time. Ova, present in large numbers in mature proglottides, remain viable for weeks and during this period they may be consumed by the intermediate host. The larvae liberated from the ova pass into the tissues of the intermediate host, and the human disease is acquired by eating undercooked beef infected with *Cysticercus bovis*, the larval stage of *Taenia saginata* (beef tapeworm), undercooked pork containing *Cysticercus cellulosae*, the larval stage of *T. solium* (pork tapeworm). or undercooked freshwater fish containing larvae of *Diphyllobothrium latum* (fish tapeworm). The adult cestode may produce little or no intestinal upset in human beings, but knowledge of its presence, by noting segments of the worm in the faeces or on underclothing, may distress the patient. Infection with a tapeworm is easily proved by the finding of segments or, less commonly, ova on microscopic examination of the stool.

TAENIA SAGINATA

This worm may be several metres long. The scolex, the size of a pin head, as four suckers; mature segments contain a central-stemmed uterus with 15 to 20 lateral branches which are easily seen if the segments are left in w for 24 hours (Fig. 101). The ova of both *T. saginata* and *T. solium* are spher and indistinguishable microscopically. The thick outer shell has radial striati and the ovum contains six hooklets. It is about the size of a threadworm ov

Infection with *T. saginata* occurs in all parts of the world, including Brit

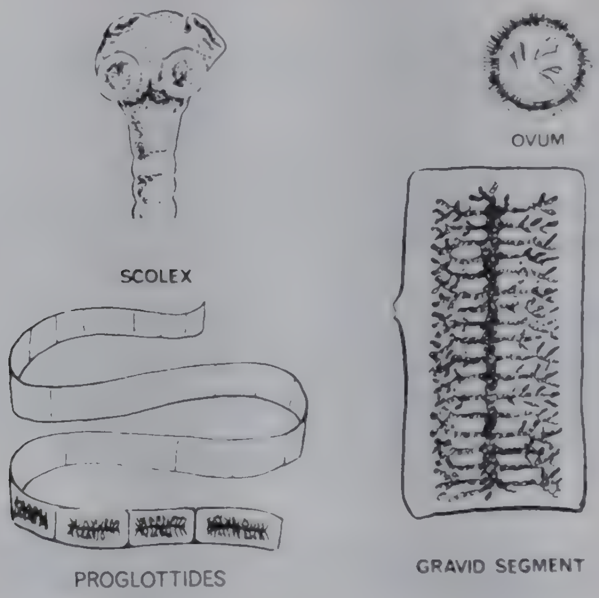


Fig. 101

Taenia saginata

Prevention. This depends on efficient meat inspection or the thorough cookin of beef.

Treatment. The drug of choice for *T. saginata* and *D. latum* is niclosamide No preparation of the patient is required other than to ensure that the bowel have been opened on the day preceding treatment. Before any food is taken in the morning, 2 tablets of the drug, each containing 0·5 g, are chewed and swallowed with a little water. One hour later a further 2 tablets are similarly taken. There are no side-effects and the worm is nearly always successfully destroyed.

TAENIA SOLIUM AND CYSTICERCOSIS

T. solium, the pork tapeworm, was formerly cosmopolitan in distribution but is now rare except in Central Europe, Ethiopia, South Africa and in certain regions of Asia. It is not so large as *T. saginata*, and the uterus has less than 14 lateral branches. The scolex has, in addition to suckers, two circular rows of hooklets anterior to the suckers. The adult worm is found only in man, but the larval cysticercus stage, which normally occurs in the pig, may occasionally develop in man as the result of the ova having gained access to the human stomach by contaminated food or fingers or by regurgitation of ova from the intestine. In the stomach the shells of the ova are digested and the larvae, liberated from the eggs, penetrate the intestinal mucosa and are carried to many of the body where they develop and form cysticerci. The most common ions are the subcutaneous tissue and skeletal muscles; when superficially ed they can be palpated under the skin or mucosa as pea-like ovoid bodies. they cause few or no symptoms; however cysts may also develop in the n. About five years later the larvae die; in the brain the tissue reaction cause epileptic fits, obscure neurological disorders, personality changes occasionally internal hydrocephalus. After death of the larvae in muscles cysts calcify and this enables them to be recognised radiologically. In the in, however, much less calcification takes place and in this situation calcified ae are only occasionally demonstrated radiologically. Epileptic fits starting adult life should suggest the possibility of cysticercosis if the patient has ed in an endemic area. The subcutaneous tissue should be palpated and iological examination of the skeletal muscles for calcified cysts must be made d repeated after intervals of six months if at first negative.

Treatment. *T. solium* can be removed by filix mas administered as follows. ter a 48-hour period of bowel preparation by fluid diet and saline aperients orning and evening 2·5 ml of a fresh extract of filix mas in capsules or as an nulsion is given at 6 a.m. and again at 6.15 a.m. and 6.30 a.m.; an appro- riately smaller dose is given to a child. The patient takes only sips of water ntil 7 a.m. when for an adult 60 ml (2 fl oz) of saturated sodium sulphate olution is given. If the scolex is not passed by 9 a.m. a soap and water enema administered. Food can be offered as soon as the scolex is seen or by 9.30 .m. in any case. All motions are scrutinised to detect the scolex. Further xperience is required before niclosamide can be confidently recommended for *. solium* as disintegration of a segment might possibly release viable ova with he risk of cysticercosis.

Treatment of cysticercosis of the brain is essentially the same as for idiopathic pilepsy; sedatives and anticonvulsants should be given to tide the patient over he period until the reaction in the brain has subsided. Most patients treated n these lines make a good recovery. Operative intervention is seldom indicated.

Prevention. Prevention of *T. solium* infection consists in having pork well ooked before consumption. Cysticercosis is avoided if food is not contaminated y ova or segments and if there is no regurgitation of gravid segments or ova rom the duodenum into the stomach as may occur from vomiting in a patient arbouring an adult *T. solium*. Great care must be taken by nurses and others to void contaminating the hands with ova from the patient.

Echinococcus Granulosus (Taenia Echinococcus)

(*Hydatid Disease*)

This is the smallest tapeworm of medical importance. The larval stage, a ydatid cyst, usually occurs in sheep and cattle. Dogs, by ingesting these cysts, re the most important definitive hosts, and a man, after handling a dog, may wallow ova excreted by the dog. The embryo is liberated from the ovum in ne small intestine and gains access to the blood stream; it develops most frequently in the liver, but sometimes in the lung or elsewhere. The resulta cyst grows very slowly.

In man a hydatid cyst is typically acquired in childhood and it may, aft growing for some years, cause pressure symptoms. These will vary, dependir on the organ or tissues involved. In nearly 75 per cent of patients with hydat disease the right lobe of the liver is invaded and contains a single cyst. I others a cyst may be found in the lung, brain, orbit or elsewhere. The diagnos depends on the clinical and radiological findings in a patient who has lived i close contact with dogs. Intradermal (Casoni) and complement-fixation test may give useful support to the diagnosis.

Treatment. When the cyst is causing pressure symptoms, surgical removal o the cyst and its laminated membrane is required. A significant advance utilise cryotherapy. A steel cone is frozen on to the organ overlying the cyst. The cyst membranes and contents are then removed through the cone and 0·5 per cen silver nitrate solution is applied to the cavity, followed by irrigation with istonic saline. Cysts in a long bone usually necessitate amputation.

Sir JAMES BAIRD.
F. J. WRIGHT.

Further reading:

Wright, F. J. & Baird, J. P. (1974). *Tropical Diseases*, 5th ed.: Supplement to *Davidson's Principles and Practice of Medicine*, 11th ed. Edited by Macleod, J. Edinburgh and London: Churchill Livingstone.

Hargreaves, W. H. & Morrison, R. J. G. (1965). *The Practice of Tropical Medicine.* London: Staples.

Macfarlane, L. R. S. (1969). *A Short Synopsis of Human Protozoology and Helminthology*, 2nd ed. Edinburgh and London: Churchill Livingstone.

Maegraith, B. G. & Gillies, H. M. (1971). *Management and Treatment of Tropical Diseases*, 1st ed. Oxford: Blackwell.

Saidi, F. & Nazarian, I. (1971). Surgical treatment of hydatid cysts. *New England Journal of Medicine*, **284**, 1346.

Wilcocks, C. & Manson-Bahr, P. E. C. (1972). *Manson's Tropical Diseases*, 17th ed. London: Ballière, Tindall and Cassell.

DIETS

The diet sheets that follow have been constructed to illustrate the quantitative and qualitative spects of diets required for the treatment of various diseases. The quantities given in a andard diet sheet will obviously require some modification in relation to the size, age, sex nd occupation of the patient. In the dietetic treatment of most diseases it is unnecessary to eigh accurately the amounts of the different foods eaten. Under these circumstances sufficient ccuracy will be secured by the use of household measures as illustrated in Diet 4 and by he terms 'small', 'medium' or 'large' helping for meat, fish or chicken. A small helping eighs approximately 1 to 2 oz (30-60 g), a medium helping 2 to 3 oz (60-90 g) and a large elping 4 oz (120 g) or more.

DIET 1

SEMI-FLUID LOW-ROUGHAGE DIET

suitable for patients who have

DIFFICULTY IN CHEWING OR SWALLOWING OR WHO ARE SEVERELY ILL WITH ULCERATIVE OR MALIGNANT DISEASE OF THE ALIMENTARY TRACT

Approximately 2,500 kcal (10·5 MJ) and 90 g of protein.

Early morning	Fruit juice with sugar.
8 a.m.	Strained porridge with milk or cream from allowance.* Coffee with fortified milk or cream and sugar from allowance.
10 a.m.	Milk shake or egg flip or Carnation Instant Breakfast Food.
12 noon	Strained cream soup. Savoury custard—using cheese, very finely minced chicken, ham, pounded white or smoked fish, *or* scrambled eggs, *or* omelette.
2 p.m.	Sweet made with puréed fruit, cream and sugar, *or* small helping of mousse or cold soufflé, *or* ice-cream with fruit, chocolate or butterscotch sauce, *or* jelly made with fruit juice, gelatine and sugar—served with cream.
4 p.m.	Coffee made with fortified milk or cream and sugar from allowance, *or* fortified milk flavoured with yeast or vegetable extract.
6 p.m.	Milk pudding with puréed fruit *or* sweet as at 2 p.m.
8 p.m.	Savoury custard as at lunch *or* scrambled or poached egg *or* omelette. Creamed potato and/or strained vegetable, e.g. Heinz. Coffee with milk or cream and sugar from allowance.
10 p.m.	Proprietary preparation of chocolate, Horlicks or Ovaltine made with fortified milk. Fruit juice with sugar or glucose to drink as desired.

* *Allowance for day:* 1 pint (0·5 *l*) of whole milk.
1 pint (0·5 *l*) of whole milk fortified with 2 oz (60 g) of full cream dried milk powder.
3 oz (90 g) sugar, or more if desired.

Management:
When necessary, the calories can be increased by adding more cream, butter or sugar.

DIET 2

INSTRUCTIONS FOR PATIENTS WITH DYSPEPSIA OR PEPTIC ULCER

1. Take four meals a day.
2. Take your meals at regular times.
3. Eat your meals slowly; chew your food carefully.
4. Avoid rush and hurry before and after meals. Rest for a few minutes before and after eating.
5. See that you get sufficient sleep at night.
6. Remember that anxiety and worry can upset digestion.
7. Avoid large, heavy meals, fried foods and any article of food which you find disagrees with you.
8. Avoid foods which are mechanically irritating or chemically stimulating (see list below) and very hot or very cold foods.
9. Do not smoke or drink alcohol before meals, when the stomach is empty.
10. Drink only sparingly at meals for this will help to ensure proper mastication, but drink plenty of water between meals.
11. Consult your dentist at regular intervals.

The following foods should be avoided during the acute stage of dyspepsia and taken sparingly during intermissions by those liable to frequent attacks of dyspepsia. For those who suffer from dyspepsia only occasionally, no special restrictions may be necessary; by trial and error the patient can find out which of the articles listed below should be avoided:

1. Alcohol, strong tea and coffee, gravies and soups made from meat extracts.
2. Raw vegetables, celery, cucumber, onions, radishes, watercress, tomatoes, mushrooms.
3. Raw unripe fruit and dried fruit (e.g. currants, raisins and figs), nuts, and the pips, skins and peel of all fruits, whether cooked or in puddings, cakes or jam.
4. Pickles, spices and condiments.
5. Tough, twice-cooked, or highly seasoned meats, including sausages, bacon and pork.
6. Salted fish and some fatty fish such as herring, mackerel, salmon and sardines.
7. Rich and heavy puddings.
8. Fried foods.
9. New bread and scones, hot buttered toast, wholemeal bread or biscuits, rye or wheat crispbread, coarse cereals, pastry, cakes containing dried fruit or peel.
10. Excess sugar and sweets.
11. Any food that the individual patient finds to be indigestible.

The following foods are permitted:

1. Milky tea or milk drink, e.g. Ovaltine.
2. Dairy products i.e., milk, cream, butter, cream cheese, eggs (not fried).
3. Fish—white fish, steamed, baked or grilled.
4. Meat—chicken, lean ham, tender beef, mutton or lamb.
5. Crisp toast (buttered cold), rusks and white bread (not new).
6. Plain biscuits and cakes, e.g. sponge cake. Honey, golden syrup, jellies.
7. Cereals—refined and well cooked, e.g. cornflour, semolina, ground rice and oatflour porridge.
8. Puddings—junket, jellies, custards, blancmange, soufflé, mousse.
9. Vegetables—potatoes, e.g. creamed or mashed, and green and yellow vegetables finely sieved and puréed with butter.
10. Fruits—stewed and preferably sieved, and served as purées or fools, raw ripe bananas and fruit juices, diluted with water, or used in jellies.

DIET 3

HIGH ROUGHAGE DIET

suitable for patients with

DIVERTICULAR DISEASE OR ATONIC CONSTIPATION

Early morning	Glass of orange juice, tea or coffee.
Breakfast	Oatmeal porridge with milk or cream, *or* bran cereal, e.g. All Bran, shredded wheat. Egg, bacon, sausage. Wholemeal bread (may be toasted) or oatcakes or crispbread. Chunky marmalade or jam. Tea or coffee.
Mid-day meal	Vegetable soup, including plenty of chopped fresh vegetables, dried peas and beans, lentils and barley. Helping of any kind of meat or fish. Large helping of vegetables. Potatoes baked in jackets. Fresh or stewed fruit *or* pudding made with dried fruit or nuts *or* wholemeat biscuits, e.g. Digestive biscuits, or oatcakes with cheese. Tea or coffee.
Evening meal	Helping of any kind of meat or fish. Large helping of vegetables or salad. Wholemeal bread *or* oatcake *or* wholemeal scone with cheese or jam if desired. Fruit, fresh or stewed. Tea or coffee.
Bedtime	Glass of hot water.
Take liberally	Vegetables, fruit, fresh or stewed, and nuts.

Note.—Unprocessed bran may help bowel habit return to normal. Try taking 1 teaspoon morning and evening. If this is insufficient gradually increase the dose until normal bowel habit is restored.

DIET 4

LOW CALORIE (ENERGY) DIET

suitable for patients with

OBESITY

(with or without diabetes)

Approximately: Protein 60 g, Carbohydrate 100 g, Fat 40 g, Energy 1,000 kcal (4·2 MJ).

Early morning	Cup of tea, milk from allowance,* if desired.
Breakfast	1 egg or 1 oz (30 g) grilled lean bacon (2 rashers) *or* cold ham *or* breakfast fish $\frac{2}{3}$ oz (20 g) white or brown bread, *or* exchange, with butter from allowance. Tea or coffee, with milk from allowance.
Mid-morning	Tea or coffee, with milk from allowance, or 'free' drink from Group A3. 1 cream cracker with butter from allowance.
Mid-day meal	Clear soup, tomato juice or grapefruit, if desired. Small helping, 2 oz (60 g) lean meat, ham, poultry, game or offal *or* 3 o (90 g) fish (steamed, baked or grilled) *or* 2 eggs *or* 2 oz (60 g) cheese. Salad or vegetables from Group A1 as desired. $1\frac{1}{3}$ oz (40 g) bread (white or brown) or exchange, with butter from allowance if desired. 1 portion of fruit from list below or 2 cream crackers with butter from allowance Tea or coffee with milk from allowance.
Mid-afternoon or bedtime	$\frac{2}{3}$ oz (20 g) white or brown bread, *or* exchange, with butter from allowance. Salad vegetables from Group A1 if desired.
Evening meal	Clear soup, meat or yeast extracts, tomato juice or grapefruit, if desired. Small helping, 2 oz (60 g) lean meat, ham, poultry, game or offal *or* 3 oz (90 g) fish (steamed, baked or grilled) *or* 2 eggs *or* 2 oz (60 g) cheese. Salad or vegetables from Group A1 as desired. $1\frac{1}{3}$ oz (40 g) bread (white or brown) *or* exchange, with butter from allowance if desired. 1 portion of fruit from list below or 2 cream crackers with butter from allowance. Tea or coffee with milk from allowance.
Before bed	Tea or coffee with milk from allowance.

* *Allowance for day:* $\frac{1}{2}$ pint milk (300 ml) with the cream poured off the top. (The use of whole milk will increase the caloric content of this diet to approx. 1,100 kcal.)

$\frac{1}{2}$ oz (15 g) butter or margarine. (Cut a $\frac{1}{2}$ lb packet into 16 equal portions, each portion = $\frac{1}{2}$ oz.)

Exchanges for $\frac{2}{3}$ oz (20 g) bread ($\frac{1}{2}$ slice from a large cut loaf):

2 cream crackers. 2 water biscuits.	$1\frac{1}{2}$ of any crispbread.	1 potato (the size of a hen's egg). 1 portion of fruit (from list below). 1 triangular oatcake.

Exchanges for $1\frac{1}{3}$ oz (40 g) bread (1 slice from a large cut loaf):

4 cream crackers. 4 water biscuits.	3 of any crispbread.	2 potatoes (size of hen's egg). 2 portions of fruit (from list below). 2 triangular oatcakes.

Fruit to be taken as part of diet at lunch or evening meal:

1 piece of fresh fruit, i.e. apple, pear, orange, peach or medium sized helping of fruit stewed without sugar.

Note.—This diet can be used as a weighed diet or as an unweighed diet by using household measures as described above.

DIET 4—*continued*

Group A: Foods which may be taken as desired

1. *Vegetables*

Artichoke, asparagus, aubergine, French beans, runner beans, broccoli, Brussels sprouts, cabbage, carrots, cauliflower, celeriac, celery, chicory, courgette, cucumber, endive, leeks, lettuce, mushrooms, mustard and cress, onions, parsley, pumpkin, radishes, salsify, seakale, spinach, swede, tomatoes, turnip, turnip tops, vegetable marrow, watercress.

2. *Fruits* (stewed without sugar, or raw)

Gooseberries, grapefruit, lemon, melons (cantaloupe, water or honeydew), rhubarb, blackcurrants, red currants, blackberries, strawberries and raspberries.

3. *Drinks*

Water, soda water, tea or coffee (without milk or sugar), lemon juice, P.L.J., tomato juice, diabetic fruit squash, Marmite, Bovril, Oxo, clear soup (chicken or beef cubes may be used).

4. *Miscellaneous*

Saxine, saccharine or any proprietary sweetening agents except Sucron and sorbitol. Salt, pepper, mustard, vinegar, herbs, spices, gelatine, Worcester Sauce, flavourings and colourings may be used.

Group B: Foods to be avoided

Sugar (brown or white), glucose, sorbitol.
Sweets, toffees, chocolates, cornflour, custard powder.
Jam, marmalade, lemon curd, syrup, honey, treacle.
Tinned, frozen or bottled fruits.
Dried fruits, e.g. dates, figs, prunes, apricots, sultanas, currants, raisins, bananas, grapes.
Cakes, buns, pastries, pies, steamed or milk puddings.
Sweet or chocolate biscuits, scones.
Cereals, e.g. rice, sago, macaroni, barley, spaghetti, etc.
Breakfast cereal, porridge.
Cocoa, Ovaltine, Horlicks, etc.
Ice cream, fresh or synthetic cream. Table jelly.
Evaporated or condensed milk.
Peas, parsnips, beetroot, sweetcorn, Haricot beans, butter beans, broad beans, lentils.
Nuts.
Salad cream, salad dressing, mayonnaise.
Tomato and brown sauce or any thickened sauce.
Sweet pickles and chutney.
Thickened soups, gravies, Bisto.
Alcoholic drinks, e.g. beer, wine, sherry, spirits.
Sweetened fruit juices, fruit squash, Coca Cola and other sweet, fizzy, ‘soft drinks’.
Lemonades, Lucozade, Ribena.
Starch-reduced products, ‘diabetic’ foodstuffs.
Sausages.
All Fried Foods.

All foods must be served without thickened gravies and sauces. Meats may be roasted. All foods may be baked, grilled, boiled or steamed—*but not fried.*

DIABETIC DIETS

METHOD OF CONSTRUCTING A DIET RESTRICTED IN CARBOHYDRATE CONTAINING APPROXIMATELY 1,800 KCAL (7·5 MJ) WITH 180 g CARBOHYDRATE, 80 g PROTEIN AND 80 g FAT

suitable for adults with

DIABETES MELLITUS

Each *carbohydrate exchange* contains approximately 10 g carbohydrate, 1·5 g protein a 0·3 g fat. Calorie value is about 50 (equivalent to ⅔ oz bread). Use is made of the Atwa calorie conversion factors of 4, 4 and 9 kcal/g for carbohydrate, protein and fat respective

Each *protein exchange* contains approximately 7 g protein and 5 g fat. Calorie value is abo 70 (equivalent to 1 oz meat).

Each *fat exchange* contains approximately 12 g fat and almost no carbohydrate or protei Calorie value is about 110 (equivalent to ½ oz butter). One pint of milk contains approximate 30 g carbohydrate, 18 g protein and 24 g fat. Calorie value is about 410.

In practice, for quick construction of a diabetic diet it is usually only necessary to wor in terms of grams of carbohydrate and total calories. For this purpose the calorie value the exchanges can be rounded to the nearest 10, i.e.

1 carbohydrate exchange = 50 kcal
protein exchange = 70 kcal
fat exchange = 110 kcal
one pint of milk = 410 kcal

Thus, a diet prescription for 180 g carbohydrate, 1,800 kcal would be calculated as follows:

1. The daily intake of carbohydrate (180 g) represents 18 carbohydrate exchanges.
2. The daily allowance of milk is decided either on the basis of the patient's food habit or on his special requirements. In this example it is 1 pint, which contains 3 carbohydrate exchanges, leaving 15 for distribution throughout the day.
3. The daily allowance of protein is then decided. Six protein exchanges will provide 420 kcal.
4. The calories allocated so far amount to 1,580; a further 220 kcal are needed to bring the total up to 1,800 kcal. This must be provided by fat. As one fat exchange provides 110 kcal, two are needed.

Exchanges	Grams of carbohydrate	kcal
1 pint milk = 3 carbohydrate exchanges	30	410
15 carbohydrate exchanges	150	750
6 protein exchanges	...	420
Total	180	1,580
2 fat exchanges	...	220
GRAND TOTAL	180	1,800

5. Finally the exchanges (15 carbohydrate, 6 protein and 2 fat) are distributed throughout the day according to the eating habits and daily routine of the patient. Diet 5 shows a specimen menu and a list of sample exchanges is shown on pp. 991 and 993.

DIETARY EXCHANGES FOR DIABETICS

1. CARBOHYDRATE EXCHANGES

Each item on this list = 1 carbohydrate exchange (10 g CHO).
Calorie value is approximately 50.

	Amount		Remarks
	oz	g	
Bread, Biscuits and Scones—			
Bread (white or brown)	⅔	20	½ slice off a large, cut loaf
Bread (toasted)	½	15	...
Scones, rolls and oatcakes	⅔	20	...
Cream crackers, crispbreads Digestive biscuits Rich Tea biscuits Water biscuits	½	15	...
Pastry (unsweetened)	⅔	20	...
Cereals—			
Porridge	4	120	Cooked
Breakfast cereals Arrowroot, barley, cornflour, custard powder, oatmeal, flour, macaroni, rice, sago, semolina, spaghetti, tapioca	½	15	All in dry state
Rice, macaroni, spaghetti	1½	45	Boiled
Spaghetti in tomato sauce	3	90	Tinned
Miscellaneous—			
Cocoa	1	30	...
Ovaltine, Horlicks, etc.	½	15	...
Creamed (tinned or packet) soup	4	120	Small teacup
Ice cream (Lyons or Wall's)	2	60	1 Small plain
Packet jelly	2	60	Made up
Milk, fresh	7	210	⅓ pint
Milk, evaporated	3	90	...
Milk, condensed (sweetened)	⅔	20	...
Ale, lager and draught beer	1 pint	600	...
Stout (Guinness)	½ pint	300	...
Vegetables—			
Potatoes (raw or boiled)	2	60	...
Potatoes (roast or chipped)	1	30	...
Potato crisps	⅔	20	...
Baked beans Butter beans Haricot beans Sweet corn Tinned peas	2	60	...
Fresh or frozen peas Beetroot	4	120	...
Parsnip	3	90	...

CARBOHYDRATE EXCHANGES—*continued*

Each item = 1 Carbohydrate exchange (10 g CHO), approx. 50 kcal.

	Raw		Stewed (without sugar)	
	oz	g	oz	g
Dried Fruits—				
Apricots	⅔	20	2	60
Figs	⅔	20	2	60
Prunes	1	30	2	60
Dates	½	15	...	...
Currants				
Sultanas				
Raisins				
Fresh Fruits—				
Apples (with skin)	4	120	5	150
Bananas (with skin)	3	90	...	...
Blackcurrants	5	150	7	210
Blackberries (brambles)	6	180	7	210
Cherries	3	90	4	120
Damsons	4	120	6	180
Grapes	2	60	...	...
Oranges and tangerines:				
—with skin	6	180	...	...
—without skin	4	120	...	...
Orange juice	4	120	...	...
Peaches	4	120	...	...
Pears	5	150	5	150
Pineapple (fresh)	3	90	...	...
Plums	4	120	7	210
Raspberries	6	180	7	210
Strawberries	6	180	...	...

2. PROTEIN EXCHANGES

Each item on this list = 1 protein exchange.
Calorie value is approximately 70.

	Amount		Remarks
	oz	g	
Meat, poultry, game and offals	1	30	Cooked weight
Corned beef, corned mutton, tinned meat	1	30	...
Meat paste and pâté	1½	45	...
Egg (1)	2	60	...
Cheese	1	30	...
Fish—white, smoked, cured, oily, shell or tinned and tripe	1½	45	Cooked weight
Sausages (include 1 carbohydrate exchange)	2	60	Cooked weight

Gravies should not contain cornflour or flour. Avoid frying as much as possible.

DIETARY EXCHANGES FOR DIABETICS—*continued*

3. Fat Exchanges

Each exchange contains approximately 12 g fat and almost no carbohydrate or protein.

Calorie value is approximately 110.

	Amount		Remarks
	oz	g	
utter, margarine, lard, dripping, cooking fat, olive oil, vegetable oil	½	15	...
ream (single)	2	60	...
ream (double)	1	30	...
alad cream or mayonnaise . . .	1	30	...

Instructions for Diabetics—*continued*

Group A: Foods which may be taken in any quantity

ea, coffee (milk from allowance, no sugar), Oxo, Bovril, Marmite, etc.
omato juice, lemon juice, P.L.J.
iabetic fruit squashes.
accharine, Saxine and Sweetex.
lear soup.
erbs, seasonings and spices.
russels sprouts, cabbage, carrots, cauliflower, celery, cucumber, French beans, leeks, lettuce, mushrooms, mustard or cress, onions, spring onions, runner beans, swedes, spinach, tomatoes, turnips, watercress.
ranberries, grapefruit, gooseberries, lemon, melon, loganberries, redcurrants, rhubarb.

Group B: To be taken in strict moderation in consultation with the Doctor

pirits, dry wines, dry sherries.

Group C: Foods not allowed

ugar, glucose, sweets, chocolate, honey, syrup, treacle, jam, marmalade, cakes, biscuits (except those specified), pies, fruit tinned in syrup, fruit squash, lemonade, or similar aerated drinks.

Note.—Most 'Diabetic' foodstuffs on sale at chemists and health food stores *do* contain me carbohydrate and must therefore *not* be taken without consulting your doctor or dietitian.

AN EXAMPLE OF THE DISTRIBUTION OF EXCHANGES FOR A DIET RESTRICTED IN CARBOHYDRATE

suitable for adults with

DIABETES MELLITUS

Approximately: Protein 80 g, Carbohydrate 180 g, Fat 80 g, Energy 1,800 kcal (7·5 MJ

Breakfast	1 protein exchange.* 4 carbohydrate exchanges.* Butter and milk from allowance.† Tea or coffee (no sugar).
Mid-morning	1 carbohydrate exchange. Butter and milk from allowance. Tea or coffee (no sugar).
Mid-day meal	Clear soup if desired. 3 protein exchanges. 4 carbohydrate exchanges. Vegetables if desired (Group A, p. 989). Butter and milk from allowance.
Mid-afternoon	1 carbohydrate exchange. Butter and milk from allowance. Tea (no sugar).
Evening meal	2 protein exchanges. 4 carbohydrate exchanges. Vegetables if desired (Group A, p. 989). Tea or coffee (no sugar).
Before bed	1 carbohydrate exchange. Remainder of butter and milk from allowance.

* A list of suitable exchanges is given on pages 991 to 992.

† *Allowance for day:* 1 pint (0·5 *l*) whole milk.
1 oz (30 g) butter or margarine.

DIET 5

AN EXAMPLE OF

A MENU RESTRICTED IN CARBOHYDRATES, BASED ON DISTRIBUTION OF EXCHANGES

suitable for patients in Britain with

DIABETES MELLITUS

Approximately: Protein 80 g, Carbohydrate 180 g, Fat 80 g, Energy 1,800 kcal (7·5 MJ).

Breakfast	4 oz (120 g) porridge with milk from allowance.* 1 egg. 2 oz (60 g) bread with butter from allowance.* Tea or coffee with milk from allowance.
Mid-morning	½ oz (15 g) Rich Tea biscuit. Tea or coffee with milk from allowance.
Mid-day meal	Clear soup with shredded vegetables. 3 oz (90 g) lean meat. 4 oz (120 g) boiled potatoes. 2 oz (60 g) tinned peas. Salad or other unrestricted vegetables from Group A if desired. 4 oz (120 g) orange (peeled weight). Milk from allowance with coffee.
Mid-afternoon	½ oz (15 g) Digestive biscuits. Tea or coffee with milk from allowance.
Evening meal	3 oz (90 g) fish. Tomato or other unrestricted vegetables from Group A if desired. 2 oz (60 g) bread with butter from allowance. 4 oz (120 g) raw apple. Tea or coffee with milk from allowance.
Before bed	Remainder of milk from allowance and ½ oz Ovaltine *or* ¾ oz bread and butter from allowance.

* *Allowance for day:* 1 pint milk (0·5 *l*).
1 oz (30 g) butter or margarine.

DIET 6

UNMEASURED DIET

suitable for patients in Britain with

DIABETES MELLITUS

Patients who are unable to weigh their diet or for whom this is unnecessary, are given list of foods which are grouped into three categories.

The following list of foods is used in the Dietetic Department of the Royal Infirma Edinburgh.

I. *Foods to be avoided altogether.*

1. Sugar, glucose, jam, marmalade, honey, syrup, treacle, tinned fruits, sweets, chocola lemonade, glucose drinks, proprietary milk preparations and similar foods which are sweeten with sugar.
2. Cakes, sweet biscuits, chocolate biscuits, pies, puddings, thick sauces.
3. Alcoholic drinks unless permission has been given by the doctor.

II. *Foods to be eaten in moderation only.*

1. Breads of all kinds (including so-called 'slimming' and 'starch-reduced' breads, brow or white, plain or toasted).
2. Rolls, scones, biscuits and crispbreads.
3. Potatoes, peas and baked beans.
4. Breakfast cereals and porridge.
5. All fresh or dried fruit.
6. Macaroni, spaghetti, custard and foods with much flour.
7. Thick soups.
8. Diabetic foods.
9. Milk.

III. *Foods to be eaten as desired.*

1. All meats, fish, eggs.
2. Cheese.
3. Clear soups or meat extracts, tomato or lemon juice.
4. Tea or coffee.
5. Cabbage, Brussels sprouts, broccoli, cauliflower, spinach, turnip, runner or French beans, onions, leeks or mushrooms. Lettuce, cucumber, tomatoes, spring onions, radishes, mustard and cress, asparagus, parsley, rhubarb.
6. Herbs, spices, salt, pepper and mustard.
7. Saccharine preparations for sweetening.

For overweight diabetics butter, margarine, fatty and dried foods must be restricted.

DIET 7

LOW SODIUM, LOW CALORIE DIET

suitable for patients with

SEVERE CARDIAC FAILURE

Approximately: Sodium 40 mEq (1 g approx.), Protein 40 g, Energy 900 kcal (3·8 MJ).

eakfast	1 thin slice of crisp toast.[1] Butter and milk from allowance.[2] Weak freshly made tea.
id-morning	Small glass of fruit juice.
id-day meal	Small helping of white fish, chicken, sweetbreads or rabbit. 1 tablespoonful of sieved vegetable. Small helping of milk pudding made with milk from allowance.
Mid-afternoon	1 thin slice of very crisp toast. Butter and milk from allowance. Weak freshly made tea.
Supper	Egg custard made with milk from allowance. Small helping of sieved fruit.
Bedtime	Milk drink made with remainder of milk from allowance.

No salt to be used in cooking or on patient's tray.

---

[1] Made from 'salt-free' bread.
[2] *Allowance for day:* $\frac{3}{4}$ pint (0·45 *l*) of milk.
$\frac{1}{2}$ oz (15 g) of butter.

DIET 8

LOW SODIUM DIET

suitable for patients who have

HEART FAILURE WITH OEDEMA
NEPHROTIC SYNDROME WITH MARKED OEDEMA[1]
CIRRHOSIS OF THE LIVER WITH ASCITES AND OEDEMA[1]

Approximately: Sodium 20 mEq (0·5 g), Protein 60 g, Carbohydrate 250 g, Fat 60 g, Energy 1,800 kcal (7·5 MJ).

Breakfast	Fruit or fruit juice, sweetened as desired. 1 egg or small helping of white fish. 1½ thin slices of 'salt-free' bread,[2] which may be toasted. Marmalade or honey. 'Salt-free' butter and milk from allowance.* Tea or coffee, with milk from allowance and sugar if desired.
Mid-morning	Tea or coffee with milk from allowance *or* fruit *or* fruit juice.
Mid-day meal	No soup. Small helping of tender meat, chicken, tripe, liver, sweetbread or white fish. Helping of vegetables. Helping of mashed or creamed potato or rice. Fruit (fresh, stewed or tinned) *or* jelly *or* whip made with egg white.
Mid-afternoon	1½ thin slices of 'salt-free' bread, which may be made into sandwiches usin tomato, apple, banana, jam or honey. Home-made biscuit to which no bicarbonate of soda, salt, baking powde or salt butter has been added. 'Salt-free' butter and milk from allowance. Tea with milk from allowance and sugar if desired.
Evening meal	1 egg *or* small helping of meat *or* fish as at mid-day meal. Fruit (fresh, stewed or tinned). 1½ thin slices of 'salt-free' bread. Jam, jelly or honey. 'Salt-free' butter and milk from allowance. Tea or coffee with milk from allowance and sugar, if desired.

* *Allowance for day:* ½ pint (0·25 *l*) of milk.
1 oz (30 g) 'salt-free' butter or margarine.

Management:

No salt to be used in cooking or at table.

Avoid all cured meat and fish, e.g. bacon, ham, tongue, pickled brisket and silverside, smoked haddock, kippers, sardines, pilchards, smoked salmon; all tinned foods except fruit; cheeses; bottled sauces, pickles, sausages and all foods made with bicarbonate of soda or baking powder, e.g., biscuits and shop cakes.

To increase the calories the following may be added: sugar, fruit, jam, marmalade and boiled sweets and pastilles.

A limit must be put on the time during which a patient may be expected to remain on this *low sodium diet*. This is usually about three to six weeks. By this time if there is no clinical improvement perseverance is useless and other therapeutic measures must be tried.

[1] In the nephrotic syndrome and cirrhosis of the liver a high protein intake (120 g) is usually required. This is most easily obtained, without increasing the sodium intake significantly, by adding to the diet 60 g of a preparation of milk protein (e.g. Casilan, Glaxo or Lonolac, Mead-Johnson).

[2] Use only bread which has been made without salt, and butter or margarine to which no salt has been added. Do not exceed the amounts of bread, milk or butter allowed, as the so-called 'salt free' bread and butter do contain a certain amount of sodium. 'Salt free' bread contains about 1 mEq Na/100 g compared with about 10 mEq Na/100 g (average) in ordinary bread.

DIET 9

VERY LOW FAT, HIGH CARBOHYDRATE DIET

suitable for patients with

ACUTE PARENCHYMAL DISEASE OF THE LIVER
SEVERE OBSTRUCTIVE JAUNDICE
TYPE 1 HYPERLIPOPROTEINAEMIA

Approximately: Protein 80 g, Carbohydrate 400 g, Fat 20 g, Energy 2,100 kcal (8·8 MJ).

Early morning	Fruit juice, with glucose or sugar.
Breakfast	Strained porridge or breakfast cereal with milk from allowance.* 1 slice of bread—may be toasted. Marmalade, jam or honey. Tea with milk and sugar from allowance.
Mid-morning	Fruit juice with sugar or coffee made with milk from allowance.
Mid-day meal	Small helping of very lean tender meat, poultry, liver, sweetbreads, tripe, lean ham or white or smoked fish. Helping of sieved vegetables. Helping of mashed potato. Cereal pudding made with milk from allowance. Fruit (fresh, stewed or tinned).
Mid-afternoon	2 slices of bread or plain biscuits. Jam, jelly or honey. Tea with milk and sugar from allowance.
Evening meal	2 slices of bread or plain biscuits. Jam, jelly or honey. Cereal pudding made with milk from allowance. Fruit (fresh, stewed or tinned). Tea or coffee with milk and sugar.
Bedtime	Milk drink *or* fruit juice with sugar.

* *Allowance for day:* ½ pint (0·25 *l*) of skimmed milk—for use in tea.
1 pint (0·5 *l*) of skimmed milk with 2 oz dried skimmed milk powder.
2 oz (60 g) sugar, or more if desired.

Management:
Take liberally fruit juice with sugar or glucose throughout day.

Avoid: Butter, margarine, dripping, cooking fat, lard and any foods including them. Fat of meat, fatty meat such as goose, duck, pork, or bacon or tinned meat. Fatty fish such as herring, kippers, bloaters, mackerel, sardines, pilchards and salmon. Oils, cream, egg yolk, salad cream, ice-cream, sauces made with fat. Pastry, pies, pudding other than milk pudding. Cakes, chocolates, sweets containing fat such as toffee, fudge or tablet. Fried foods and the use of fat in cooking.

DIET 10

CHOLESTEROL-LOWERING DIET

suitable for patients with

PRIMARY HYPERCHOLESTEROLAEMIA (TYPE II HYPERLIPOPROTEINAEMIA)

Low in saturated fats and cholesterol with increased amounts of polyunsaturated fat.

Foods to be avoided.

Butter and hydrogenated margarines. Use polyunsaturated margarine, e.g. 'Flora'.
Lard, suet, shortenings and cakes, biscuits and pastries made with these.
Fatty meat and visible fat on meat. Meat pies, sausages and luncheon meats.
Whole milk and cream and commercial cream toppings.
Chocolate, ice cream (except water ices).
Cheese, except low fat cottage cheese.
Coconut, coconut oil and 'Coffee Mate'.
Eggs—no more than 1 to 2 egg yolks per week, including that used in cooking.
Organ meats—liver, kidneys and brain.
Shellfish and fish roes.
Fried foods unless fried in polyunsaturated oil (like sunflower or corn oil).
Potato crisps and most nuts.
Gravy unless made with polyunsaturated oil, and tinned soups.
Salad dressing unless made with polyunsaturated oil.

Foods freely allowed.

Bread, white and wholemeal, toast, crispbreads and plain biscuits.
Breakfast cereals, porridge and pasta.
Potatoes and rice.
All vegetables, salads and fruit (fresh, stewed, tinned and dried).
Fish, white and fatty (baked or fried in polyunsaturated oil).
Lean meat, preferably chicken and veal.
Jam, marmalade, honey, sugar, jellies, condiments and spices.
Tea, coffee, fruit juice and carbonated beverages.
Polyunsaturated oils like sunflower and corn oil, and margarine, e.g., 'Flora'.
Skimmed milk.
Cottage cheese.
Meringues and cakes and biscuits made with egg white and polyunsaturated fat.

Sample Menu, energy approx. 2,000 kcal (8·4 MJ).

Breakfast Citrus fruit or juice.
Cereal or porridge, skimmed milk and sugar.
Toast.
Polyunsaturated margarine and marmalade.
Coffee or tea with skimmed milk.

Mid-day meal Sardines or tuna fish.
Potatoes.
Salad.
Fruit or allowed dessert or bread and jam.
Tea with skimmed milk.

Evening meal Poultry, fish or lean, trimmed meat.
Rice or pasta.
Vegetables.
Fruit or allowed dessert.
Digestive biscuits and cottage cheese.
Coffee.

DIET 11

HIGH PROTEIN, LOW FAT DIET

suitable for patients with

Subacute or Chronic Pancreatic Disease[1]
Subacute Parenchymal Liver Disease with Jaundice
Severe Obstructive Jaundice (Recovering)
Tropical Sprue[1]
Idiopathic Steatorrhoea[2]

Approximately: Protein 120 g, Carbohydrate 350 g, Fat 45 g, Energy 2,300 kcal (9·6 MJ).

reakfast	Helping of breakfast cereal with milk from allowance* and fresh or stewed fruit *or* fruit juice. 1 egg *or* 2 rashers of lean bacon, grilled and drained of fat, *or* piece of white fish. Crisp toast or bread. Marmalade, jam, honey *or* syrup. Tea or coffee with milk and sugar from allowance.
Mid-morning	Cup of coffee or milk drink with milk and sugar from allowance.
Mid-day meal	Tomato or fruit juice *or* extracts of yeast, meat or vegetables. Large helping of very lean meat or fish. Helping of sieved vegetables. Potatoes, boiled, mashed or baked. Fruit, fresh, tinned or stewed, made into jelly or whipped with egg white. Milk pudding with milk from allowance. Tea or coffee with milk and sugar, if desired.
Mid-afternoon	Sandwiches with filling of egg, chicken, lean ham, cheese or very lean meat. Tea with milk and sugar from allowance.
Evening meal	Large helping of very lean meat or fish. Vegetables. Potato. Helping of milk pudding with fruit *or* bread with jam, honey or syrup. Tea or coffee with milk from allowance.
Bedtime	Proprietary milk drink with milk from allowance. 1 plain biscuit.

* *Allowance for day:* 2 pints (1 *l*) of skimmed milk.
2 oz (60 g) sugar, more if desired to increase calories.

Management:

Foods to be avoided—Butter, margarine, lard, dripping, cooking fat, fat of meat, tinned meat or fatty fish; foods incorporating fat in cooking, e.g. pastry, suet puddings, cakes, sauces, soups, fried food; cream, ice-cream, nuts, chocolate, caramels, toffee.

Foods suitable—Sugar, boiled sweets, fruit, jam, marmalade, honey, syrup, jelly. Very lean meat—except pork; poultry—except goose and duck; liver, kidney, tripe, heart, rabbit, hare, very lean ham, white or smoked fish. Egg—boiled, poached or baked, or made into custard with skimmed milk. Cheese—not cream cheese. Sieved vegetables, flower of cauliflower, tomato without skins or pips, asparagus tips. Sauce may be made for meat, fish or vegetables with skimmed milk, flour, and grated cheese, hard-boiled egg or parsley. No fat to be used.

[1] In those cases of the sprue syndrome and subacute and chronic pancreatic disease in which acid frothy stools indicate an intolerance to starch, the amount of starchy foods (porridge, bread, cereal products and potatoes) in this diet should be reduced.

[2] Idiopathic steatorrhoea does not include coeliac disease since the latter is a gluten induced enteropathy in which bread or other wheaten or rye products should be avoided entirely (Diet No. 15).

DIET 12

HIGH-PROTEIN, RESTRICTED SODIUM DIET

suitable for patients with

THE NEPHROTIC SYNDROME
CIRRHOSIS OF THE LIVER WITHOUT JAUNDICE AND ASCITES

Approximately: Protein 90 g or more, Energy 2,400 kcal (10 MJ).

Early morning	Tea or coffee with milk from allowance* *or* fruit juice.
Breakfast	Porridge *or* cereal *or* stewed fruit with milk from allowance *or* fruit juice. 2 eggs—poached, boiled or scrambled—or a portion of white fish. Bread—may be toasted. Marmalade or honey. Butter and milk from allowance. Tea or coffee.
Mid-morning	Coffee or milk drink made with milk from allowance. Plain biscuit.
Mid-day meal	Large helping of any kind of lean meat, poultry, game, liver, kidney, trip sweetbreads or unsalted white fish. Helping of vegetables. Helping of potato—boiled, mashed or baked. Light sweet, incorporating milk and egg if possible. Fruit—fresh, stewed, or tinned as desired.
Mid-afternoon	Sandwiches with filling of scrambled or sieved hard-boiled egg, minced mea or chicken. Butter and milk from allowance. Tea—sugar if desired.
Evening-meal	Large helping of meat as at mid-day meal or 2 eggs scrambled, as omelette, etc Vegetables if desired. Bread with butter from allowance. Jam, jelly or honey or milk pudding with fruit. Tea or coffee with milk from allowance.
Bedtime	Milk drink. Plain biscuit.

* *Allowance for day:* 1 pint (0·5 *l*) of milk.
1 oz (30 g) low salt butter or margarine.

Management:

The intake of salt must be restricted by not adding table salt, by using minimal amounts in cooking, and by avoiding salt-rich foods.

The protein intake can be increased by incorporating 'Casilan' into some of the dishes, e.g. ½ oz with mid-day meal and again with evening meal (1 oz provides 26 g of protein).

DIET 13

LOW PROTEIN DIET

suitable for patients with

SEVERE ACUTE GLOMERULONEPHRITIS (RECOVERING)
CHRONIC RENAL DISEASE WITH MARKED NITROGEN RETENTION

Approximately: Protein 40 g, Carbohydrate 250 g, Fat 60 g, Energy 1,700 kcal (7·1 MJ).

Breakfast	Fruit (fresh or stewed) or small glass of fruit juice. 1½ thin slices of bread, which may be toasted. Marmalade or honey. Butter and milk from allowance.* Tea with sugar.
Mid-morning	Cup of tea or coffee with milk and sugar from allowance. 1 biscuit.
Mid-day meal	Small helping of meat *or* poultry or fish or 2 eggs scrambled or baked. Small helping of vegetables. 1 medium-size potato. Milk pudding, using milk from allowance and sugar. Fruit (fresh, stewed or tinned).
Mid-afternoon	2 thin slices of bread with jam, jelly or honey, or may be made into sandwiches, using tomato, lettuce, cucumber, dates or banana. Butter and milk from allowance. Cup of tea.
Evening meal	1 slice of bread or 2 plain biscuits. Jam, jelly or honey. Fruit (fresh, stewed or tinned). Butter and milk from allowance. Tea or coffee with milk from allowance and sugar.

* *Allowance for day:* ½ pint (0·25 *l*) of milk.
1¼ oz (37 g) butter or margarine.

For patients with acute glomerulonephritis some restriction of fluid is necessary. No more than one cup of tea should be allowed on each occasion. Salt should not be used in cooking, nor should table salt be allowed.

For patients with renal failure and nitrogen retention but without oedema, restriction of fluid intake is strongly contraindicated.

DIET 14

RESTRICTED PROTEIN DIET

suitable for patients with

CHRONIC RENAL FAILURE OF MODERATE SEVERITY

Approximately: Protein 50-60 g, Carbohydrate 280 g, Fat 100 g, Energy 2,300 kcal (9·6 M

Breakfast	Cornflakes or similar cereal with fruit and milk from allowance.* 1 egg, poached, boiled or scrambled, *or* 2 rashers of bacon *or* small helpi of fish. 2 slices of bread or toast. Marmalade or honey. Butter and milk from allowance. Tea or coffee with milk from allowance and sugar.
Mid-morning	Tea or coffee with milk from allowance and sugar, *or* fruit juice with glucos 1 plain biscuit.
Mid-day meal	Small helping of any kind of meat, poultry, game or fish. Helping of vegetables. Helping of potato. Milk pudding with milk from allowance. Fruit (fresh, stewed or tinned).
Mid-afternoon	2 slices of bread which may be made into sandwiches, using tomato, cucumber, lettuce, dates, banana, jam, jelly or honey. Butter and milk from allowance. Tea.
Evening meal	1 egg, poached, boiled, scrambled or as omelette with filling of tomato, asparagus or spinach, *or* baked egg with tomato or asparagus, *or* small helping of macaroni cheese *or* fish kedgeree *or* fish cake. Vegetables if desired. Milk pudding with milk from allowance, *or* fruit (fresh, stewed or tinned). 2 slices of bread or toast. Jam, jelly or honey. Butter and milk from allowance. Tea or coffee.

* *Allowance for day:* $\frac{3}{4}$ pint (0·45 *l*) of milk.
2 oz (60 g) butter or margarine.

No salt to be added at table and the minimum used in cooking if hypertension or oedema is present.

DIET 15

GLUTEN-FREE DIET

suitable for patients with

COELIAC DISEASE

mple Menu.

akfast	Fruit. Cornflakes or Rice Krispies. Egg and bacon. Gluten-free bread, with butter and marmalade. Tea or coffee with milk and sugar.
id-day meal	Meat or fish—any gravy to be thickened with cornflour. Vegetables, avoiding those prepared with mayonnaise or sauce. Potatoes. Special pudding made with gluten-free flour *or* fruit.
vening meal	Soup made with meat or vegetable stock and thickened with gluten-free flour, lentils, potato, etc. Egg *or* cheese *or* meat *or* fish dish. Potatoes or rice. Vegetables. Special pudding made with gluten-free recipe. Milk. Coffee.
Bedtime	Milk drink. Gluten-free biscuits.

The following foods contain gluten and are forbidden.

All Bran, baking powder, bread, biscuits, cakes (unless made with pure wheat starch), crispbreads, scones, toast, breakfast cereals (except those listed below), ice cream (except makes isted below), liquorice sweets, macaroni, malted milk, noodles, packet and pudding mixtures, pastry mixtures, patent infant foods, meat pies, proprietary sauces and ketchups, puffed wheat, rusks, sausages, semolina, Shredded Wheat, spaghetti, tinned soups, meats, vermicelli, wheat flakes.

The following foods, being free of gluten, can be included in the diet.

Baked beans, boiled sweets, certain breakfast cereals—cornflakes, Post Toasties, Puffed Rice, Rice Krispies, Sugar Ricicles; butter, cheese, chocolate, cornflour, custard powder, eggs, fish, ruits and fruit juices, squashes, honey, ice cream (made by Wall's, Lyons, Eldorado), jams, marmalade, meat (fresh), milk, oatmeal* (in moderation), poultry, rice, sago, soya flour, ugar, tapioca, vegetables (all kinds, including potatoes).

A full current list of gluten-free foods and recipes can be obtained from The Coeliac Society, P.O. Box No. 181, London, NW2 2QY.

Note.—Some coeliacs cannot tolerate oats and barley.

Table 17

Weights for Age—Birth to 5 Years, sexes combined[1]

	Weight (kg)				Weight (kg)		
Age (months)	Standard[2]	80% Std	60% Std	Age (months)	Standard[2]	80% Std	60% Std
0	3·4	2·7	2·0				
1	4·3	3·4	2·5	31	13·7	11·0	8·2
2	5·0	4·0	2·9	32	13·8	11·1	8·3
3	5·7	4·5	3·4	33	14·0	11·2	8·4
4	6·3	5·0	3·8	34	14·2	11·3	8·5
5	6·9	5·5	4·2	35	14·4	11·5	8·6
6	7·4	5·9	4·5	36	14·5	11·6	8·7
7	8·0	6·3	4·9	37	14·7	11·8	8·8
8	8·4	6·7	5·1	38	14·85	11·9	8·9
9	8·9	7·1	5·3	39	15·0	12·05	9·0
10	9·3	7·4	5·5	40	15·2	12·2	9·1
11	9·6	7·7	5·8	41	15·35	12·3	9·2
12	9·9	7·9	6·0	42	15·5	12·4	9·3
13	10·2	8·1	6·2	43	15·7	12·6	9·4
14	10·4	8·3	6·3	44	15·85	12·7	9·5
15	10·6	8·5	6·4	45	16·0	12·9	9·6
16	10·8	8·7	6·6	46	16·2	12·95	9·7
17	11·0	8·9	6·7	47	16·35	13·1	9·8
18	11·3	9·0	6·8	48	16·5	13·2	9·9
19	11·5	9·2	7·0	49	16·65	13·35	10·0
20	11·7	9·4	7·1	50	16·8	13·5	10·1
21	11·9	9·6	7·2	51	16·95	13·65	10·2
22	12·05	9·7	7·3	52	17·1	13·8	10·3
23	12·2	9·8	7·4	53	17·25	13·9	10·4
24	12·4	9·9	7·5	54	17·4	14·0	10·5
25	12·6	10·1	7·6	55	17·6	14·2	10·6
26	12·7	10·3	7·7	56	17·7	14·3	10·7
27	12·9	10·5	7·8	57	17·9	14·4	10·75
28	13·1	10·6	7·9	58	18·05	14·5	10·8
29	13·3	10·7	8·0	59	18·25	14·6	10·9
30	13·5	10·8	8·1	60	18·4	14·7	11·0

[1] Based on table by Jelliffe (1966).

[2] Boston standards (Stuart & Stevenson, 1959), taking mean of boys and girls. Boys are 0·05 to 0·15 kg heavier and girls 0·05 to 0·15 kg lighter.

TABLE 18

DESIRABLE WEIGHTS OF ADULTS
According to height and frame.

Height without shoes			Desirable weight in kilograms and pounds (in indoor clothing), ages 25 and over					
			Small frame		Medium frame		Large frame	
metres	ft	in	kg	lb	kg	lb	kg	lb
			Men					
1·550	5	1	50·8-54·4	112-120	53·5-58·5	118-129	57·2-64	126-141
1·575	5	2	52·2-55·8	115-123	54·9-60·3	121-133	58·5-65·3	129-144
1·600	5	3	53·5-57·2	118-126	56·2-61·7	124-136	59·9-67·1	132-148
1·625	5	4	54·9-58·5	121-129	57·6-63	127-139	61·2-68·9	135-152
1·650	5	5	56·2-60·3	124-133	59 -64·9	130-143	62·6-70·8	138-156
1·675	5	6	58·1-62·1	128-137	60·8-66·7	134-147	64·4-73	142-161
1·700	5	7	59·9-64	132-141	62·6-68·9	138-152	66·7-75·3	147-166
1·725	5	8	61·7-65·8	136-145	64·4-70·8	142-156	68·5-77·1	151-170
1·750	5	9	63·5-68	140-150	66·2-72·6	146-160	70·3-78·9	155-174
1·775	5	10	65·3-69·9	144-154	68 -74·8	150-165	72·1-81·2	159-179
1·800	5	11	67·1-71·7	148-158	69·9-77·1	154-170	74·4-83·5	164-184
1·825	6	0	68·9-73·5	152-162	71·7-79·4	158-175	76·2-85·7	168-189
1·850	6	1	70·8-75·7	156-167	73·5-81·6	162-180	78·5-88	173-194
1·875	6	2	72·6-77·6	160-171	75·7-83·5	167-185	80·7-90·3	178-199
1·900	6	3	74·4-79·4	164-175	78·1-86·2	172-190	82·7-92·5	182-204
			Women					
1·425	4	8	41·7-44·5	92-98	43·5-48·5	96-107	47·2-54	104-119
1·450	4	9	42·6-45·8	94-101	44·5-49·9	98-110	48·1-55·3	106-122
1·475	4	10	43·5-47·2	96-104	45·8-51·3	101-113	49·4-56·7	109-125
1·500	4	11	44·9-48·5	99-107	47·2-52·6	104-116	50·8-58·1	112-128
1·525	5	0	46·3-49·9	102-110	48·5-54	107-119	52·2-59·4	115-131
1·550	5	1	47·6-51·3	105-113	49·9-55·3	110-122	53·5-60·8	118-134
1·575	5	2	49 -52·6	108-116	51·3-57·2	113-126	54·9-62·6	121-138
1·600	5	3	50·3-54	111-119	52·6-59	116-130	56·7-64·4	125-142
1·625	5	4	51·7-55·8	114-123	54·4-61·2	120-135	58·5-66·2	129-146
1·650	5	5	53·5-57·6	118-127	56·2-63	124-139	60·3-68	133-150
1·675	5	6	55·3-59·4	122-131	58·1-64·9	128-143	62·1-69·9	137-154
1·700	5	7	57·2-61·2	126-135	59·9-66·7	132-147	64 -71·7	141-158
1·725	5	8	59 -63·5	130-140	61·7-68·5	136-151	65·8-73·9	145-163
1·750	5	9	60·8-65·3	134-144	63·5-70·3	140-155	67·6-76·2	149-168
1·775	5	10	62·6-67·1	138-148	65·3-72·1	144-159	69·4-79	153-174

Based on weights of insured persons in the United States associated with lowest mortality (*Statist. bull. Metrop. Life Insur. Co.*, 40, Nov.-Dec. 1959).

NOTES ON INTERNATIONAL SYSTEM OF UNITS (SI UNITS)

Examples of Basic SI Units

Length	metre (m)
Mass	kilogram (kg)
Amount of substance	mole (mol)
Energy	joule (J)
Pressure	pascal (Pa)

Examples of Decimal Multiples and Submultiples of SI Units

Factor	*Name*	*Symbol*
10^{6}	mega-	M
10^{3}	kilo-	k
10^{-1}	deci-	d
10^{-2}	centi-	c
10^{-3}	milli-	m
10^{-6}	micro-	μ
10^{-9}	nano-	n
10^{-12}	pico-	p

Units of Volume and Concentration.

Volume. The basic SI unit of volume is the cubic metre (1,000 litre). Because of its convenience the litre is used as the unit of volume in laboratory work.

Amount of Substance ('*Molar*') *Concentration* (e.g., mol/*l*, μmol/*l*) is used for substances of defined chemical composition. It replaces equivalent concentration (mEq/*l*) which is not part of the SI system—for reporting measurements of sodium, potassium, chloride and bicarbonate. The numerical value of these measurements is unchanged.

Mass Concentration (e.g., g/*l*, μg/*l*) is used for all protein measurements, for substances which do not have a sufficiently well defined composition and for plasma vitamin B_{12} and folate measurements. The numerical value in SI units will change by a factor of 10 in those instances previously expressed in terms of 100 ml.

Haemoglobin is an exception. It is agreed internationally that meantime haemoglobin should continue to be expressed in terms of g/dl (g/100 ml).

Non-SI units are employed for enzymes and immunoglobulins.

Nomograms of Metric Equivalents.

Nomograms giving the metric equivalents for measurements, in other systems, of volume, weight, length and temperature are shown on page 1012.

BIOCHEMICAL AND HAEMATOLOGICAL VALUES

B = Blood F = Faeces P = Plasma S = Serum U = Urine		Reference Values *Approximate normal ranges (adults)*		Multiplication factor for converting from other units to SI units
		SI Units	Other Units	
B	Ammonium	23-47 μmol/*l*	40-80 μg/100 ml	0·587
B	Ascorbate	45-80 μmol/*l*	0·8-1·4 mg/100 ml	56·8
U	Ascorbate	114-284 μmol/24 h	20-50 mg/24 h	5·68
B	Base Excess	± 2 mmol/*l*	± 2 mEq/*l*	No change
P	Bicarbonate	24-32 mmol/*l*	24-32 mEq/*l*	No change
P	Bilirubin (total)	5-17 μmol/*l*	0·3-1·0 mg/100 ml	17·1
S	Caeruloplasmin	300-600 mg/*l*	30-60 mg/100 ml	10
P	Calcium (total)	2·12-2·62 mmol/*l*	8·5-10·5 mg/100 ml	0·250
U	Calcium	2·5-7·5 mmol/24 h	100-300 mg/24 h	0·0250
B	Carbon dioxide (P_{CO_2})	4·5-6·1 kPa	34-46 mm Hg	0·133
P	β-Carotene	0·9-5·6 μmol/*l*	50-300 μg/100 ml	0·0186
U	Catecholamines (as adrenalin)	0·05-0·55 μmol/24 h	10-100 μg/24 h	0·00546
P	Chloride	95-105 mmol/*l*	95-105 mEq/*l*	No change
P	Cholesterol	3·6-7·8 mmol/*l*	140-300 mg/100 ml	0·0259
P	Copper	13-24 μmol/*l*	80-150 μg/100 ml	0·157
U	Copper	0·2-0·8 μmol/24 h	10-50 μg/24 h	0·0157
U	Coproporphyrins	0·15-0·31 μmol/24 h	100-200 μg/24 h	0·00153
P	Cortisol	276-690 nmol/*l*	10-25 μg/100 ml	27·6
U	Creatine	0-400 μmol/24 h	0-50 mg/24 h	7·69
P	Creatinine	62-124 μmol/*l*	0·7-1·4 mg/100 ml	88·4
U	Creatinine	9-17 mmol/24 h	1·0-2·0 g/24 h	8·84
F	Fat (as stearic acid)	11-18 mmol/24 h	3-5 g/24 h	3·52
P	Fibrinogen	1·5-4·0 g/*l*	150-400 mg/100 ml	0·01
S	Folate	3-20 μg/*l*	3-20 ng/ml or μmg/ml	No change
B	Glucose	2·5-4·7 mmol/*l*	45-85 mg/100 ml	0·0555
B	Haemoglobin	14·4 g/dl	14·4 g/100 ml or g%	No change
S	Haptoglobins (Hb binding)	0·3-2·0 g/*l*	30-200 mg/100 ml	0·01
U	5-Hydroxyindole acetate (5 HIAA)	16-73 μmol/24 h	3-14 mg/24 h	5·24
U	4-Hydroxy 3-methoxy mandelate (HMMA)	10-35 μmol/24 h	2-7 mg/24 h	5·05
U	Hydroxyproline	0·08-0·27 mmol/24 h	10-35 mg/24 h	0·00763
S	Iron	14-29 μmol/*l*	80-160 μg/100 ml	0·179
S	Total iron binding capacity (as iron)	45-72 μmol/*l*	250-400 μg/100 ml	0·179
B	Lactate	0·4-1·4 mmol/*l*	3·6-13·0 mg/100 ml	0·111
B	Lead	0·5-1·9 μmol/*l*	10-40 μg/100 ml	0·0483
B	Leucocytes (total) (WBC)	4·0-11·0 × 10^9/*l*	4,000-11,000/μl or 4·0-11·0 × 10^3/mm^3	10^6

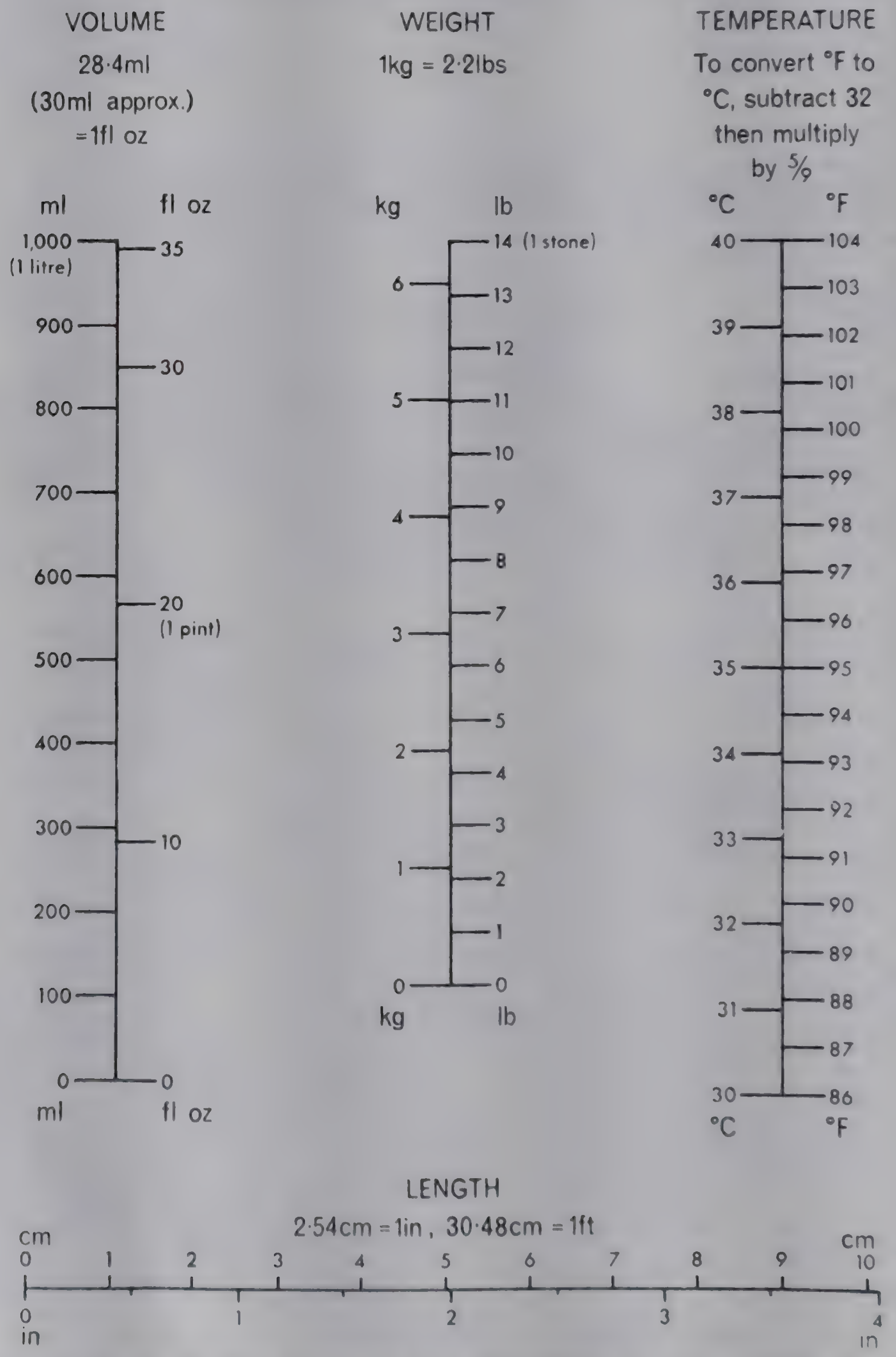
BIOCHEMICAL AND HAEMATOLOGICAL VALUES—*continued*

B = Blood F = Faeces P = Plasma S = Serum U = Urine		Reference Values *Approximate normal ranges (adults)*		Multiplicati factor for convertin from othe units to SI units
		SI Units	Other Units	
P	Lipids (total)	4·0-10·0 g/l	400-1,000mg/100ml	0·01
P	Magnesium	0·7-1·0 mmol/l	1·8-2·4 mg/100 ml	0·411
U	Magnesium	3·3-4·9 mmol/24 h	80-120 mg/24 h	0·0411
B	Mean Corpuscular Haemoglobin (MCH)	27-32 pg	27-32 pg or μμg	No change
B	Mean Corpuscular Haemoglobin Concentration (MCHC)	30-35 g/dl	30-35%	No change
B	Mean Corpuscular Volume (MCV)	75-95 fl	75-95 μ^3 or μm^3	No change
F	Nitrogen	71-143 mmol/24 h	1-2 g/24 h	71·4
P	Non-protein nitrogen	14-21 mmol/l	20-30 mg/100 ml	0·714
U	Oestriol	(7-173) μmol/24 h	(2-50) mg/24 h	3·47
B	Oxygen (Po_2)	12-15 kPa	90-110 mm Hg	0·133
U	17 Oxogenic steroids (as dehydro-epi-androsterone	35-69 μmol/24 h	10-20 mg/24 h	3·47
U	17-Oxosteroids (as dehydro-epi-androsterone)	35-87 μmol/24 h	10-25 mg/24 h	3·47
B	Packed Cell Volume (PCV)	0·41	41%	0·01
B	Platelets	150-400 × 10^9/l	150,000-400,000/μl or/mm^3	10^6
S	Phenylalanine	42-73 μmol/l	0·7-1·2 mg/100 ml	60·5
P	Phosphate (as inorganic P)	0·8-1·4 mmol/l	2·5-4·5 mg/100 ml	0·323
U	Phosphate (as inorganic P)	16-48 mmol/24 h	0·5-1·5 g/24 h	32·3
U	Porphobilinogen	0·9-8·8 μmol/24 h	0·2-2 mg/24 h	4·42
P	Potassium	3·8-5·0 mmol/l	3·8-5·0 mEq/l	No change
U	Pregnanediol	0-3·1 μmol/24 h	0-1 mg/24 h	3·12
U	Pregnanetriol	0·3-8·9 μmol/24 h	0·1-3 mg/24 h	2·97
S	Proteins—total	62-82 g/l	6·2-8·2 g/100 ml	10·0
S	—albumin	36-52 g/l	3·6-5·2 g/100 ml	10·0
S	—globulins	24-37 g/l	2·4-3·7 g/100 ml	10·0
CSF	Proteins	0·1-0·4 g/l	10-40 mg/100 ml	0·01
S	Protein bound iodine	315-590 nmol/l	4·0-7·5 μg/100 ml	78·8
B	Pyruvate	45-80 μmol/l	0·4-0·7 mg/100 ml	113
B	Red Cell Count (RBC)	4·5 × 10^{12}/l	4·5 × 10^6/μl or/mm^3	10^6
B	Red Cell Diameter	6·7-7·7 μm	6·7-7·7 μ or μm	No change
B	Reticulocytes	0·2-2·0% or 10-100 × 10^9/l	0·2-2·0% or 10-100 × 10^3/μl	No change 10^6

BIOCHEMICAL AND HAEMATOLOGICAL VALUES—*continued*

B = Blood F = Faeces P = Plasma S = Serum U = Urine		Reference Values *Approximate normal ranges (adults)*		Multiplication factor for converting from other units to SI Units
		SI Units	Other Units	
P	Sodium	136-148 mmol/*l*	136-148 mEq/*l*	No change
S	Thyroxine-iodine	244-465 nmol/*l*	3·1-5·9 μg/100 ml	78·8
S	Transferrin	1·2-2·0 g/*l*	120-200 mg/100 ml	0·01
P	Triglyceride (as triolein)	0·28-1·69 mmol/*l*	25-150 mg/100 ml	0·0113
P	Urate	0·12-0·42 mmol/*l*	2-7 mg/100 ml	0·0595
U	Urate	3-12 mmol/24 h	0·5-2·0 g/24 h	5·95
B	Urea	2·5-6·6 mmol/*l*	15-40 mg/100 ml	0·166
U	Urea	250-500 mmol/*l*	1·5-3·0 g/100 ml	166
F	Urobilinogen	50-504 μmol/24 h	30-300 mg/24 h	1·68
P	Vitamin A	0·7-1·7 μmol/*l*	20-50 μg/100 ml	0·0349
S	Vitamin B_{12} (as cyanocobalamin)	160-925 ng/*l*	160-925 pg/ml or $\mu\mu$g/ml	No change
B	Xylose	(0·33-3·33) mmol/*l*	(5-50) mg/100 ml	0·0667
U	Xylose	(1·3-26·6) mmol	(0·2-4·0) g	6·66

NOMOGRAMS OF METRIC EQUIVALENTS



Nomograms giving the metric equivalents for measurements, in other systems, of volume, weight, length and temperature.

dex

A

domen, examination of, 436
ducent nerve, 816
ortion, genetic factors in, 12
ortus fever, 78
bscess, cerebral, 853
  pelvic, 501
  perinephric, 602
  pulmonary, 349
  spinal epidural, 855
  subphrenic, 505
cetest tablets, 683
chalasia of the cardia, 452
chlorhydria, 441
choluric jaundice, 736
Achondroplasia, 627
Acid-base equilibrium, 198, 581
Acid excretion, by kidney, 585
Acidosis, metabolic, 201
  respiratory, 204
Acoustic neuroma, 822
Acromegaly, 626
ACTH, 654, 669
Actinomycosis, 373
  penicillin in, 96
Acute abdomen, 500
Adams-Stokes syndrome, 238
Addiction to drugs, 912, 933
Addisonian crisis, 661
Addisonian pernicious anaemia, 728
Addison's disease, 660
Adenoma, bronchial, 404
Adenovirus pneumonia, 346
Adrenal cortex, hormones of, 654
Adrenal cortical insufficiency, 659
Adrenal failure, idiopathic, 36, 37
Adrenal glands, anatomy and physiology, 654
  hyperfunction, 655
Adrenal haemorrhage, 660
Adrenal insufficiency, congenital, 663
  investigation of, 663
  secondary, 662
Adrenal medulla, hormones of, 671
Adrenaline, 40, 379, 671
Adrenergic beta-receptor, antagonists, 235
  stimulants, 378
Adrenocorticotrophic hormone (ACTH), 654
  ectopic, 657
Aerography, 435
Agammaglobulinaemia, Bruton type, 27
  Swiss type, 27
Agnosia, 809
Agranulocytosis, 744
Albuminuria, 586
Alcoholism, 912, 932
  dementia in, 941
  fibrosis of liver in, 556
  Korsakoff's psychosis in, 482
  pancreatitis in, 482
  polyneuropathy in, 901
  self-poisoning and, 948
Aldosterone, 655
Aldosteronism, 659
Alimentary tract, infections of, 521
  psychogenic disorders of, 522
  vascular disorders of, 521
Alkaline phosphatase, 138, 534
  stain in chronic myeloid leukaemia, 751
Alkalosis, hypokalaemic, 190
  metabolic, 202
  respiratory, 204
Alkylating agents, in leukaemia, 749
Alleles, 4
Allergy, 15
  of respiratory tract, 373
Allografts, 16
Allopurinol, in gout, 785
Alpha-fetoprotein, 537
Alveolitis, allergic, 382
  fibrosing, 407
Amantadine, 876
Amblyopia, nutritional, 169
  tobacco, 815
Amiloride, 196, 250
Amino acids, the essential, 116
Aminoglycosides, 102
Aminophylline, 40, 379
Aminoquinolines, in malaria, 967, 969
Amnesia, and dementia, 941
Amoebiasis, 970
Amoebic abscess of liver, 971
Amoeboma, 971
Amoxycillin, 98
Amphetamine addiction, 934
Amphetamine poisoning, 954
Amphotericin B, 104
Ampicillin, 97
Amylase, serum, 481
Amyloidosis, in myelomatosis, 756
  in rheumatoid arthritis, 770
  of liver, 557
  renal disease and, 595
Amyotrophic lateral sclerosis, 881
Anaemia, aplastic, 734
  classification of, 720
  clinical features of, 721
  dimorphic, 730

Anaemia—*continued*
  due to blood loss, 724
  due to hepatic fibrosis, 742
  due to infection, 741
  due to pyridoxine deficiency, 164
  haemolytic, 735
    and methyldopa, 38
    autoimmune (acquired), 32, 855
    from drugs, 738
    from *Vicia faba*, 738
    of newborn, 738
    symptomatic, 740
  hypochromic, chronic nutritional, 722
    in infancy and childhood, 723
    in pregnancy, 724
  in heart disease, 207
  in malignancy, 742
  in myxoedema, 734
  in portal hypertension, 756
  in scurvy, 733
  in uraemia, 741
  iron deficiency, 722
  leuco-erythroblastic, 720
  megaloblastic, causes of, 727
    due to drugs, 728, 733
    in infancy, 733
    nutritional, 731
  nutritional, in tropics, 166
  of uncertain origin, 741
  pernicious, 32, 728
  sideroblastic, 164, 727
Analgesics, 773
  and neuropathy, 620
Anaphylactic reaction, 28-31
Ancylostoma duodenale, 976
Ancylostomiasis, 976
  and anaemia, 724
Anencephaly, 14
Aneuploidy, 10
Aneurysm, cerebral, 848
  dissecting, of aorta, 303
  syphilitic, of aorta, 305
Angina pectoris, 268
Angiocardiography, 223
Angio-oedema, 592
Angiotensin, 582
Anisocytosis, 719
Ankylosing spondylitis, 779
Anorectic drugs, 181
Anorexia nervosa, 523, 628, 925
Anosmia, 814
Antacids, 462
Anterior poliomyelitis, 867
Anthrax, penicillin in, 96
Antibiotics, 93
  combinations of, 106
  resistance to, 44, 109
Antibodies, blocking, 40
  gastric, 32
Antibodies—*continued*
  lens, 38
  mitochondrial, 32
  reactive, with skeletal muscle, 37
  red cells, 31
  sperms and, 38
  thyroid, 32
  transmission of, across the placenta, 23
Antibody detection, 33
  complement fixation tests in, 33
  immunofluorescence in, 33
  latex particle agglutination in, 33
  precipitation test for, 33
  tanned red cell agglutination in, 33
Antibody production, 15
Anticholinergic drugs, 463
  in Parkinsonism, 875
Anticoagulants, bleeding from, 765
  in cerebral arterial disease, 845
  in myocardial infarction, 271
  in pulmonary embolism, 284
  in venous thrombosis, 309
Anticonvulsant drugs, 830
  megaloblastic anaemia due to, 728
Antidepressants, 943, 945
Antidotes, in poisoning, 952
Antigen, 15
Antihaemophilic factor, 763
Antihistamines, 39
  in hay fever, 375
Antihypertensive drugs, 279
Anti-inflammatory drugs, 41, 773
Antilymphocytic serum, 41
Antimetabolites, in leukaemia, 749
Antimicrobial agent, selection of, 105
Antimitochondrial antibody, 537
Antinuclear factor (ANF), 781
Antiserum, precautions in use of, 68
Antitetanus serum (ATS), 77
Antithyroid drugs, 636
Antitoxic sera, 59
Antivitamins, 131
Antrectomy, 464
Anuria, 583
Anxiety neurosis, 918
Aorta, aneurysm of, 303
  coarctation of, 292
Aortic regurgitation, 256
Aortic stenosis, 257
Aortic valve, bicuspid, 257
Aortic valve disease, 256
Aortitis, syphilitic, 304
Apex beat, 210
Aphasia, 810
Aphonia, hysterical, 924
Aphthous stomatitis, 445
Aplastic anaemia, 734
Appendicitis, 506
Appetite, 433

axia, 809
ovirus infections, 975
yll Robertson pupil, 860
old Chiari syndrome, 885
est, cardiac, 239
hythmias, cardiac, 225
eries, diseases of, 299
eriography, intracranial, 836
eriolar necrosis, in hypertension, 275
eriolar sclerosis, in hypertension, 275
teriosclerosis, 299
teritis, cranial, 306
giant cell, 306
tery, occlusion of, 303
thritis, causes of, 770
in rheumatic fever, 260
psoriatic, 771
rheumatoid, 768
rthus reaction, 33
rtificial respiration, 240
sbestosis, 411
scaris lumbricoides, 979
schoff nodule, 259
scites, in cardiac failure, 247
  in cirrhosis of liver, 559
  in constrictive pericarditis, 290
  malignant, 479
Ascorbic acid, 148
Asparaginase, 749
Aspergillosis, 372
Aspiration pneumonias, 346
  benign, 348
Aspirin, causing gastro-duodenal haemorrhage, 465
  in rheumatoid arthritis, 773
Astereognosis, 805
Asthma, bronchial, 29, 30, 40, 375
  cardiac, 245
  immune reactions in, 376
Asthmatic pulmonary eosinophilia, 381
Astrocytoma, 832
Ataxia, cerebellar, 800
  hereditary (Friedreich's), 884
  sensory, 804
  telangiectasia, 27
Atelectasis, 397
Atheroma. *See* Atherosclerosis
Atherosclerosis, 300
  cerebral, 842
  coronary, 265
  in diabetes mellitus, 703
  obliterans, 300
Athetosis, 799, 879
Atopy, 29
Atrial fibrillation, 228
Atrial flutter, 230
Atrial septal defect, 293
Atrial tachycardia, 231
Atrio-ventricular block, 236
Atrophy, muscular, 881, 901
  optic, 815
Auditory nerve, 822
Auscultation, of heart, 211
  of lungs, 325
Australia antigen, 537
Autoantibodies, 537
Autoimmune adrenal failure, 660
Autoimmune haemolytic anaemia, 738
Autoimmune thyroid disease, 642
Autoimmunity, 16, 38, 39
  genetic factors in, 39
  in rheumatoid arthritis, 769
  relation of drugs to, 38
  relation of infection to, 38
Automatism, 829
Autosomal trisomic states, 10
Autosomes, 3, 7, 11
Axillary vein thrombosis, 308
Azathioprine, 40
Azospermia, 674

B

B lymphocytes, 17-21
Babinski reflex, 796
Bacilluria, 588
Bacteraemia, chemotherapy of, 106
Bacterial endocarditis, 263
Bacteroides infections, lincomycin in, 101
Bagassosis, 383, 411
BAL (British Anti-Lewisite), 776
Bantu siderosis, 128, 557
Barbiturate addiction, 934
Barbiturate poisoning, 953
Barium enema, and meal, 437
Barr bodies, 4
Basophil adenoma, of pituitary, 624
BCG vaccination, 371
Bell's palsy, 821
Bence-Jones protein, 28, 755
Benign systolic murmur, 212
Benzathine penicillin, 96
Benzodiazepine poisoning, 956
Benzylpenicillin, 95
Beriberi, 153
  infantile, 155
Berylliosis, 411
Beta-adrenergic blocking drugs, 235
  in angina pectoris, 269
  in hypertension, 280
  in hyperthyroidism, 638
Bethanidine, 279
Bicarbonate, buffer system, 200
Biguanides, 691
Bile, enterohepatic circulation of, 532
Bile ducts, tumours of, 576
Bile pigment, metabolism of, 532
Bilharziasis. *See* Schistosomiasis

Biliary cirrhosis, 561
Biliary colic, 573
Biliary dyskinesia, 576
Biliary tract, diseases of, 568
Bilirubin, excretion, 535
  in urine, tests, 535
Bilirubin metabolism, effect of drugs on, 543
Biological values, 1009
Biopsy, jejunal, 493
  lung, 328
  lymph node, 328
  pleural, 328
  renal, 590
Bird fancier's lung, 383
Bitôt's spots, 134
Blackwater fever, 966
Bladder, nervous control of, 808
  tumours of, 618
Bleach poisoning, 954
Bleeding, arrest of, in haemophilia, 763
Blind loop syndrome, 494
Blindness, causes of, 135
  in diabetes mellitus, 705
Blood, cells, development, 714
  coagulation, 756
  destruction, 718
  disorders, terminology of, 718
  formation, 713
  group incompatibility, 738
  pressure, 213
  transfusion, incompatible, 740
Blood-gas analysis, 329
Boils, 63
Bone, diseases of, 790
  tumours of, 790
Bornholm disease, 788
Botulism, 73
Bovine cough, 385
Brachial neuritis, 900
Bradycardia, sinus, 226
Brain, localising signs of disease, 805
    of cerebellum, 800
    of cerebral cortex, 796, 805
    of extrapyramidal system, 799
    of internal capsule, 796
    of occipital lobe, 809
    of parietal lobe, 809
    of precentral gyrus, 809
    of prefrontal lobe, 808
    of posterior column, 804
    of spinothalamic tract, 805
    of temporal lobe, 810
    of thalamus, 805
    of upper motor neurone, 794
    of visual pathway, 812
Brain scan, 836
Brain stem, lesions of, 797, 805
Brain syndromes, organic, 939
Breath sounds, 325
Breathing, control of, 318
Brodie's abscess, 790
Bromsulphthalein excretion, 535
Bronchi, anatomy of, 313, 314
Bronchial adenoma, 404
Bronchial asthma, 375
Bronchial carcinoma, 401
Bronchial obstruction, 396
Bronchiectasis, 393
Bronchitis, acute, 339
  chronic, 387
Bronchography, 328
Bronchopleural fistula, 421
Bronchopneumonia, acute, 347
Bronchopulmonary segments, 313
Bronchoscopy, 328
Bronchus, tumours of, 401
Bronzed diabetes, 566
Brown-Séquard syndrome, 888
Brucellosis, 79
Buccal smear, 4
Buerger-Allen exercises, 302
Buerger's disease, 305
Buffer system of blood, 200
Bulbar palsy, progressive, 881
Bulbar paralysis, 867
Bullae, pulmonary, 393
Bundle branch block, 219, 239
Burning feet syndrome, 168
Bursa of Fabricius, 16
Busulphan, 751
Byssinosis, 411, 413

C

Caeruloplasmin, 876
Café au lait pallor, 264
Calabar swellings, 977
Calciferol, 136, 139
  in tetany, 654
Calcitonin, 648
Calcium, absorption, 127
  dietary sources of, 126
Calculi, biliary, 572
  renal, 613
  vesical, 613
Cancer immunology, 42
Candicidin, 104
Candida albicans, chemotherapy, 104
Candidiasis, oral, 445
Candidosis, 372
Cannabis addiction, 934
Capillaries in blood coagulation, 757, 878
Carbenicillin, 98
Carbenoxolone, 463
Carbimazole, 637
Carbohydrate, 116

bohydrate—*continued*
  etabolism, of liver, 530
bon dioxide, 198, 317
bon monoxide poisoning, 958
bonic acid, buffer system, 200
buncle in diabetes mellitus, 705
cinoid tumour, 507
rcinoma. *See* also individual organs
  eurological complications of, 897
rdiac. *See* also Heart
rdiac arrest, 239
rdiac asthma, 245
  treatment of, 251
ardiac failure, 242
ardiac massage, 240
ardiac neurosis, 298
ardiac syncope, 242
ardiac tamponade, 288
ardiogenic shock, 251
ardiomyopathy, 286
Cardiospasm, 452
Carditis, in rheumatic fever, 260
Caries, dental, 129
Carotene, 132
Carotid artery stenosis, internal, 844
Carotid sinus, hypersensitive, 242
Carpal tunnel syndrome, 900
Casoni test, 984
Casts, bronchial, 400
  urinary, 588
Cataplexy, 831
Cataract in diabetes mellitus, 705
Catheterisation, cardiac, 224
Cauda equina lesion, 888
Cell mediated (delayed) hypersensitivity,
    28, 35
Cells, monosomic, and trisomic, 10
Centromere, 3
Cephaloridine, 99
Cephalosporins, 99
Cerebellum, 799
  signs of lesions of, 800
Cerebral abscess, 853
Cerebral aneurysm, 848
Cerebral arterial thrombosis, 844
Cerebral atherosclerosis, 842
Cerebral embolism, 845
Cerebral haemorrhage, 846
Cerebral infarction, 844
Cerebral tumours, 832
  investigation of, 835
Cerebral venous thrombosis, 851
Cerebrospinal fever, 856
Cerebrospinal fluid, 852
Cerebrovascular disease, 841
Cervical disc herniation, 890
Cervical rib, 1026
Cervical symphathetic fibres, 825
Cestodes, 981
Chagas' disease, 285
  and megacolon, 520
  of oesophagus, 453
Chancre, primary, 80
Charcot's joints, 862, 885
Cheilosis, 162
Chelating agents, 877
Chemotherapy, 93
  of infections, 107
  of leukaemia, 749
  of tuberculosis, 366
  prophylactic, 108
Chest, examination of, 324
  physical signs in, 326
  radiological examination of, 327
Chest wall, deformities of, 425
Cheyne-Stokes respiration, 245
Chickenpox, 88
Children, poisoning in, 959
Chlamydia infections, of respiratory tract, 337
  tetracycline in, 100
Chlorambucil, 752
Chloramphenicol, 101
  in typhoid fever, 71
Chloroquine, in hepatic amoebiasis, 972
  in malaria, 967
  in rheumatoid arthritis, 776
Chlorpromazine, in psychiatric disorders, 943
Chlorpropamide, 691
Chlorthalidone, 195, 250
Cholangiography, 570
Cholangio-hepatitis, 561
Cholecalciferol, 136
Cholecystitis, acute, 570
  chronic, 572
Cholecystography, 438, 569
Cholelithiasis, 572
Cholera, 963, 974
Cholestatic jaundice, 540
Cholesterol and atherosclerosis, 266
Cholestyramine, 566
Cholinergic crisis, 904
Chondrocalcinosis, 786
Chorea, gravidarum, 877
  Huntington's, 7, 13, 878
  Sydenham's, 261, 877
Choreiform movements, 799
Choriomeningitis, acute lymphocytic, 859
Christmas disease, 764
Chromate, radioactive, 737
Chromatids, 2
Chromatin, sex, 4
Chromophobe adenoma, of pituitary, 624
Chromosomes, 1-14
Chvostek's sign, 653
Cigarette smoking, and bronchial carcinoma,
    401
  and chronic bronchitis, 387
  and ischaemic heart disease, 266

Cigarette smoking—*continued*
  and optic neuritis, 815
  and peripheral vascular disease, 302
Circulatory failure, peripheral, 251
Cirrhosis of the liver, 558
  biliary, 561
  cryptogenic, 32
  portal, 558
  primary biliary, 32, 562
  syphilitic, 567
  treatment, 563
Clasp-knife phenomenon, 795
Clearance, renal, 585
Cleft palate, 14
Clindamycin, 101
Clinistix, 683
Clinitest tablets, 683
Clofibrate, 273
Clonidine, in hypertension, 280
  in migraine, 841
Clonorchis sinensis, 977
Clonus, 796
Clotrimazole, 104
Clotting time, whole blood, 759
Cloxacillin, 96
Clubbing of the fingers, 324
Coalworker's pneumoconiosis, 410
Coarctation of the aorta, 292
Cobalamin, 715
Cobalt, 165
Cocaine addiction, 933
Cod liver oil, 136
Codominance, 8
Coeliac disease, 492
Colchicine, in gout, 785
Cold abscess, 357
Colectomy, for ulcerative colitis, 514
Colic, biliary, 573
  renal, 615
Colistin, 103
Colitis, ulcerative, 508
Collagen diseases, 768
Collapse, of lung, 397
Colloidal gold curve (Lange), 853
Colon, carcinoma of, 517
  polyposis of, 13
Colonoscopy, 440
Colour blindness, 8
Coma, 825
  diabetic, clinical features, 699
    distinction from hypoglycaemia, 702
    treatment, 700
  hepatic, 550
  hyperosmolar diabetic, 700
  in hypopituitarism, 628
Common cold, 335
Communicable diseases, 43
Complement, 34
Compliance, of lung, 317
Condylomata, 81
Connective tissue disorders, 768
Conn's syndrome, 659
Constipation, 435
Constrictive pericarditis, 289
Contact dermatitis, 35
Contraceptive pill, in liver disease, 544
  and venous thrombosis, 308
Coombs' test, 31
Copper metabolism, 876
Cor pulmonale, 284
Coronary artery disease, 265
Coronary care units, 272
Coronary occlusion, 186, 269
Coronary thrombosis, 267
Corrosive poisoning, 954
Cortical necrosis, renal, 607
Corticosteroids, uses and dangers of, 669,
  in bronchial asthma, 379
  in rheumatoid arthritis, 774
  in tuberculosis, 369
  in ulcerative colitis, 513
  suppression of immune response, 41
Corticotrophin, 654, 669
Cortisol, 667
Cortisol levels, in adrenal insufficiency, 66
Cortisone, 667
Coryza, 335
Co-trimoxazole, 95
Cough, 312, 320
  syncope, 242
Coumarin drugs, in venous thrombosis, 309
Coupled beats, 227
Coxiella infection, tetracycline in, 100
Coxsackie virus infection, 288, 337, 414
Craniopharyngioma, 625
Creatinine clearance, 586
Creatorrhoea in pancreatic insufficiency, 48
Crepitations, 325
Cretinism, 644
Crigler-Najjar syndrome, 542
Crisis, Addisonian, 661
  cholinergic, 904
  haemolytic, 736
  thyrotoxic, 641
Crohn's disease, 496
Croup, 336
Crush syndrome, 609
Cryoprecipitate, 763
Cryptorchism, 673
Cushing's syndrome, 656
Cyanide poisoning, 954
Cyanocobalamin. *See* Vitamin B_{12}
Cyanosis, in heart disease, 207
Cyclophosphamide, 40, 749
Cycloserine, 103
Cystic fibrosis, 351, 484
Cysticercosis, 982
Cystinuria, 582

tis, 605
abine, 105
megalic inclusion disease, 747
sine arabinoside, 749
toxic drugs, 40

D

ntigen, 738
sone, in leprosy, 974
malaria, 969
k adaptation, 134
norubicin, 749
T, 962
ath, sudden, causes of, 241
brisoquine, 279
jà vu, 810, 829
layed (cellular) hypersensitivity, 28, 35
lirium, 911, 940
elirium tremens, 932
elusion, 917
ementia, 911, 941
  in Huntington's chorea, 879
  pre-senile, 843
emyelinating diseases, 869
engue, 975
ental extraction, in haemophilia, 763
eoxyribonucleic acid, 5
epression, endogenous, 936
  reactive, 937
ermatomyositis, 781
Desensitisation, to antituberculous drugs, 368
Di George syndrome, 27
Di Guglielmo's disease, 748
Diabetes insipidus, 629
  nephrogenic, 629
Diabetes mellitus, 675
  adult onset, 680
  aetiology, 676
  chemical pathology, 677
  clinical features, 680
  coma, 699
  complications, 698
  corticosteroids and, 677
  diet in, 687
  genetic counselling, 711
  gestational, 677
  glomerulosclerosis in, 704
  in children, 706
  infections in, 705
  juvenile onset, 680
  latent, 681
  morbid anatomy, 679
  neuropathy, 706
  potential, 681
  pregnancy, 707
  prognosis, 710
  retinopathy, 704
  screening, 711
Diabetes mellitus—*continued*
  secondary, 677
  surgery, 708
  treatment, 686
  urine testing, 696
  vascular disorders, 703
Diamorphine, in myocardial infarction, 271
Diaphragm, hernia of, 449
  paralysis of, 403, 406
Diarrhoea, 435
Diazepam, 943
Diet, in cirrhosis of liver, 998, 1002
  in coeliac disease, 1005
  in coronary disease, 273
  in diabetes mellitus, 687, 990
  in diverticular disease, 987
  in dyspepsia, 986
  in glomerulonephritis, 1003
  in heart failure, 997, 998
  in hepatitis, acute, 999, 1001
  in hypercholesterolaemia, primary, 1000
  in hyperlipoproteinaemia, Types I and II, 999, 1000
  in jaundice, obstructive, 999, 1001
  in nephrotic syndrome, 998, 1002
  in obesity, 988
  in pancreatitis, chronic, 1001
  in peptic ulcer, 986
  in renal failure, 1003, 1004
  in sprue, 1001
Diffusion of gases in lungs, 320
Digitalis, 248
Digitoxin, 249
Digoxin, 248
Dihydrotachysterol, 654
Dimercaprol, in gold toxicity, 776
Dinito-ortho-cresyl poisoning, 954
Diphtheria, 65
Diphyllobothrium latum, 978, 1135
  anaemia in, 728
Diplopia, 815, 816
Disc, intervertebral, 890
Disodium cromoglycate, 39, 380
Disseminated sclerosis, 869
Diuretics, 195
  adverse effects of, 196
  in ascites, 564
  in cardiac failure, 249
  in hypertension, 280
Diverticular disease, 515
Diverticulum, traction of oesophagus, 452
DNA, 5
Dominant inheritance, 7
Down's syndrome, 12, 1059
Dracunculus medinensis, 977
Drugs, causing agranulocytosis, 744
  causing purpura, 758
  causing thrombocytopenia, 762
  dangers in rheumatic diseases, 792

Dubin-Johnson syndrome, 542
Duchenne type muscular dystrophy, 14
Ductus, arteriosus, patent, 291
Dumping syndrome, 472
Duodenoscopy, 440
Duodenum, diseases of, 455
Dupuytren's contracture, 560
Dwarfing, nutritional, 125
Dwarfism, differential diagnosis, 627
Dyes, in urine, 588
Dysarthria, 811
Dysdiadochokinesis, 800
Dysentery, amoebic, 970
  bacillary, 74
Dyshormonogenesis, 646
Dysmetria, 800
Dyspepsia, gall-bladder, 573
  management of, 986
  psychogenic, 523
Dysphagia, 448
  sideropenic, 449
Dysphasia, 810
Dysphonia, 811
Dyspnoea, 244, 321
  paroxysmal nocturnal, 245
Dyssebacea, 163
Dyssynergia, 800
Dystonia, 799
Dystrophia myotonica, 907
Dystrophy, muscular, 906
    Duchenne type, 14, 906

E

Ecchymosis, 759
Echinococcus granulosus, 983
Echocardiography, 224
Echo-encephalography, 835
Ectopic beats, 227
Edinburgh mask, 331
Edrophonium, 904
Effort syndrome, 298
Effusion, pleural, 414
Electrocardiography, 214
Electroconvulsant therapy (ECT), 937
Electroencephalography, 830, 835
Electrolytes, disturbances in, 186
Electromyography, 798
Embolism, cerebral, 845
  in infective endocarditis, 264
  paradoxical, 845
  pulmonary, 282
Emergency resuscitation, 239
Emetine, in amoebiasis, 972
Emotional disturbances, 935
Emphysema, 390
  heart disease in, 284
  mediastinal, 390
Emphysema—*continued*
  subcutaneous, 390
Empyema thoracis, 418
  tuberculous, 421
Encephalitis, 864
  benign myalgic, 866
  lethargica, 866
  suppurative, 853
  viral, 865
Encephalomyelitis, acute demyelinating,
  acute disseminated, 872
  post-vaccinial, 872
Encephalopathy, hepatic, 560
  hypertensive, 276
  in acute nephritis, 591
  Wernicke's, 896
Endocardial fibroelastosis, 286
Endocarditis, infective, 263
    penicillin in prophylaxis of, 96
  rheumatic, 260
  subacute bacterial, 263
Endomyocardial fibrosis, 286
Endoscopy, of gastrointestinal tract, 439
Enteric fever, 69
Enterobius vermicularis, 978
Enterohepatic circulation of bile salts, 48
Entrapment neuropathy, 900
Enzyme induction, 531
Enzymes, serum, in myocardial infarcti
    269
Eosinophil adenoma, of pituitary, 624
Eosinophilia, 719
  pulmonary, 381
Epidemiology of infection, 45
Epidural abscess, 855
Epilepsy, 13, 827
  focal, 829
  Jacksonian, 829
Ergocalciferol, 135
Ergotamine, in migraine, 841
Erysipelas, 62
Erythema marginatum (erythema annulare)
    261
Erythema nodosum, 261, 359
Erythraemia, 742
Erythraemia myelosis, 748
Erythroblastosis foetalis, 738
Erythrocyte sedimentation rate, 718
Erythrocytosis, 742
Erythromycin, 99, 427
Erythropoietin, 713
Ethacrynic acid, 195, 250
Ethambutol, 366
Eunuch, 673
Exchange transfusion, 739
Exercise, and coronary disease, 266
Exophthalmic ophthalmoplegia, 641
Exophthalmos, 641
Extrapyramidal disorders, 873

pyramidal system, 798
s of lesions of, 799
systoles, 227
, nutritional disorders of, 133, 163, 170

F

al nerve, 820
al paralysis, 821
or VIII, 762
or IX, 764
ting, 241
ciparum malaria, 966
ot's tetralogy, 295
nilial hypophosphataemia, 582
nilial periodic paralysis, 908
nine oedema, 114
coni syndrome, 582
rmer's lung, 34, 383, 411
sciculation, 798
t, absorption, 488
metabolism, in diabetes mellitus, 679
vism, 738
lty's syndrome, 778
nfluramine, 181
rrous salts, in anaemia, 725
etishism, 934
EV/FVC%, 328
ever, abortus, 78
  enteric, 69
  relapsing, 975
  rheumatic, 259
  sandfly, 975
  scarlet, 61
  yellow, 962, 975
ibrillation, atrial, 228
ibrin, in blood coagulation, 757
ibrinogen in blood coagulation, 757
ibrinogenopenia, 765
ibrocystic disease of pancreas, 484
ibrosing alveolitis, 407
ibrosis, pulmonary, 408
ibrositis, 788
ick formula, 225
ilariasis, 977
ilix mas, 983
its, epileptic, 827
  hysterical, 924
locculation tests, in liver disease, 534
lucloxacillin, 96
ludrocortisone, 667
luorine, 128
  in prevention of dental caries, 129
  poisoning, 129
-fluorocytosine, 104
luorosis, 129
lutter, atrial, 230
ocal nephritis, 592
Foetor hepaticus, 550
Folate, 165, 715, 727
Folate absorption, 490
Folic acid, 731, 732, 733
Food allergy, 31
Food and Nutrition Board of the USA, recommended allowances for calories, 113
Forced expiratory time (FET), 329
Forced expiratory volume (FEV), 328
Forced vital capacity (FVC), 328
Foreign body, in bronchus, 397
  in larynx, 385
Foster Kennedy syndrome, 834
Framycetin, 102
Freund's adjuvant, 22, 36, 37
Friction rub, pericardial, 288
Friedländer's pneumonia, 345
Friedreich's ataxia, 884
Froin's syndrome, 888
Fructosuria, 683.
Frusemide, 195, 250
Fucidin, 101
Fugues, hysterical, 924
Fundus, ocular, in diseases of the central nervous system, 814
  in hypertension, 276
Fungal infections, of respiratory tract, 373
Funnel chest, 425

G

Gall-bladder, anatomy and physiology, 568
  cholesterolosis of, 576
  tumours of, 576
Gallop rhythm, 212
Gall-stones, 572
  dissolution of, 575
Gamma globulin, in measles, 86
Gangrene, gas, penicillin in, 96
  in atherosclerosis, 300
  in diabetes mellitus, 704
Gas exchange in lungs, 319
Gas transfer factor, 320
Gastrectomy, 464
Gastric aspiration and lavage, 952
Gastric outlet obstruction, 468
Gastrin, 430
Gastritis, 474
  biliary, 472
Gastroenterostomy, 464
Gastrointestinal tract, absorptive system, 431
  defence mechanisms, 431
  investigation of, 436
  motility, 429
  pain, 432
  secretion, 429
Gastro-jejuno-colic fistula, 471

- Gastroscopy, 439
- Gaucher's disease, 557, 756
- Gene, 4
- General paralysis of the insane, 861
- Genetic code, 5
- Genetic counselling, 13
  - in diabetes mellitus, 711
- Genetic expression, 7
- Genetic penetrance, 7
- Geniculate herpes, 822
- Gentamicin, 102
- Geriatric patients, osteomalacia in, 142
  - osteoporosis in, 144
  - psychiatric disorders in, 941
  - scurvy in, 149
- German measles, 86
- Giantism, 626
- Gilbert's syndrome, 541
- Gingivitis, 444
- Glandular fever, 745
- Glioma, 832
- Globulin, antihaemophilic. *See* Antihaemophilic factor
- Globus hystericus, 523
- Glomerulonephritis, 32, 34, 589
  - acute, 589
  - chronic, 597
  - membranous, 594
  - minimal lesion, 594
  - poststreptococcal, 32
  - proliferative, 589
- Glossitis, 446
- Glossopharyngeal nerve, 824
- Glottis, oedema of, 385
- Glucagon, 480, 698
- Glucocorticoids, 654
- Glucose, normal levels in blood, 684
- Glucose-6-phosphate dehydrogenase deficiency, 738
  - and malaria, 967, 969
- Glucose tolerance test, 684
- Gluten-free diet, 493
- Gluten-induced enteropathy, 492
- Glyceryl trinitrate, 269
- Glycosuria, alimentary, 686
  - in diabetes mellitus, 682
  - 'lag-storage', 686
  - renal, 684
- Goitre, 645
  - simple, 647
  - toxic, 631
- Goitrogens, 647
- Gold, in rheumatoid arthritis, 776
  - toxic reactions, 776
- Gonorrhoea, 79
- Gonorrhoeal arthritis, 771
- Goodpasture's syndrome, 32, 592
- Gout, 783
- Graft rejection, 16, 35
- Grand mal epilepsy, 828
- Granulocytes, 716
- Griseofulvin, 104
- Growth hormone, and diabetes, 677
- Guanethidine, 279
- Guillaine-Barré syndrome, 902
- Guinea worm, 977
- Gumma, 81
- Gums, in scurvy, 149
- Gynaecomastia, 11

H

- Habit spasm, 881
- Haematemesis, 465
  - in portal hypertension, 564
- Haematological values, 717, 1009
- Haematuria, 587
- Haemochromatosis, 566
- Haemodialysis, 600, 611
- Haemoglobin, 715
- Haemoglobinopathies, hereditary, 737
- Haemoglobinuria, 588, 740
- Haemolytic anaemia, 735
- Haemolytic disease of the newborn, 41
- Haemophilia, 8, 762
- Haemopneumothorax, 315
- Haemoptysis, 321
  - in heart disease, 283
- Haemorrhage, gastroduodenal, 464
  - intracerebral, 846
  - subarachnoid, 849
- Haemorrhages, splinter, 264
- Haemorrhagic diseases, 756
  - classification, 758
  - of the newborn, 764
- Haemosiderosis, 567
  - pulmonary, 408
- Haemothorax, 315
- Hair, nutritional disorders of, 119, 170
- Hallucinations, 810, 917
- Haloperidol, 933, 943
- Halothane, and jaundice, 544
- Haptoglobin, 736
- Hartnup disease, 159
- Hashimoto's thyroiditis, 645
- Hay fever, 29, 40, 374
- Head injury, and coma, 826
- Headache, causes of, 838
  - in hypertension, 275
- Heaf test, 360
- Heart, conduction defects, 225
  - enlargement of, physical signs, 210
  - examination of, 210
  - output, 225
  - radiological examination of, 223
- Heart block, 235
- Heartburn, 434

t disease, congenital, 290
pregnancy, 297
evention, 310
rgical treatment, 296
rt failure, 242
beriberi, 154
ft-sided, 244
ght-sided, 246
eatment, 247
art murmurs, 212
art sounds, 211
plitting, 212
berden's nodes, 787
lminthic infections, 973
IgE in, 25
mianopia, 813
emiplegia, 844
stuttering, 844
emisphere, dominant, 805
emizygous inheritance, 8
enoch Schönlein purpura, 592, 760
eparin, in venous thrombosis, 309
lepatic amoebiasis, 971
lepatic encephalopathy, 560
lepatitis, acute infective, 546
  aggressive, 554, 557
  chronic persistent, 554, 557
  in glandular fever, 746
  serum, 548
  viral, 545
Hepatitis associated antigen (HAA), 537
Hepato-lenticular degeneration, 567, 876
Hepatomegaly, differential diagnosis, 563
Hereditary ataxia, 884
Hereditary factors, 1-14
Hereditary haemorrhagic telangiectasia, 760
Hermaphroditism, 674
Hernia, oesophageal hiatus, 449
Herniation, of cervical disc, 890
Heroin, addiction, 933
  in myocardial infarction, 271
Herpangina, 336
Herpes, simplex, encephalitis, 865
  zoster, 868
Heterozygous inheritance, 5, 8
Hiatus hernia, 449
Hirschsprung's disease, 520
Hirsutism, 657
Histamine, 31
Hodgkin's disease, 753
Homosexuality, 934
Homozygous inheritance, 5, 8
Honeycomb lung, 408
Hookworm infection, 976
Hormones, of neurohypophysis, 623
  of pituitary, 622
Horner's syndrome, 825
Hunger, 433
Huntington's chorea, 7, 13, 878
Hyaline membrane disease, 401
Hydatid cyst, 983
Hydrochloric acid, gastric, 456
Hydrocortisone, 668
  intra-articular, 775
Hydrogen ion concentration, 198
  disturbances in, 200
Hydronephrosis, 612
Hydropneumothorax, 315
Hydrops fetalis, 738
Hydrothorax, 246
Hydroxocobalamin, 715
5-Hydroxytryptamine, 507
Hyperacusis, 821
Hyperaemia, reactive, 301
Hyperbilirubinaemia, congenital, 541
Hypercalcaemia, differential diagnosis of, 650
Hypercapnia, 323
Hypercholesterolaemia, primary, diet for, 1000
Hyperglycaemia, in diabetes mellitus, 678
Hyperkalaemia, 192
Hyperlipidaemia, and coronary disease, 266
Hyperlipoproteinaemia, Type I, diet for, 999
  Type II, diet for, 1000
Hypernephroma, 617
Hyperosmolar diabetic coma, 700
Hyperparathyroidism, 649
Hyperpyrexia, 827
Hypersensitivity, cell mediated delayed, 28, 29, 35
  immediate, 28, 29
Hypersplenism, 756
Hypertension, 273
  essential, 274
  in aldosteronism, 659
  in Cushing's syndrome, 656
  in phaeochromocytoma, 671
  malignant, 277
  pulmonary, 281
  secondary, 273
Hypertensive encephalopathy, 276
Hyperthyroidism, 631
  in children, 641
  in pregnancy, 641
Hyperventilation and tetany, 652
Hypervitaminosis D, 141
Hypnotics, 944
Hypochondriasis, 920
Hypochromia, 719
Hypoglossal nerve, 824
Hypoglycaemia, coma in, distinction from diabetic coma, 702
  features, 697
  following gastrectomy, 473
  treatment, 698
Hypoglycaemic agents, oral, 691
Hypogonadism, male, 672
Hypokalaemia, 190

Hypoparathyroidism, 651
  idiopathic, 38
Hypophosphataemia, familial, 582
Hypopituitarism, 627
Hypoprothrombinaemia, 764
Hyposensitisation, 40
Hypostatic pneumonia, 348
Hypotension, postural, 241
Hypothalamic - pituitary - adrenal function, tests of, 665
Hypothalamus, anatomy and physiology of, 622
Hypothermia, 826
  in hypopituitarism, 628
  in hypothyroidism, 643
  in poisoning, 953
Hypothyroidism, 642
  in children, 643
  in infants, 644
  investigation of, 644
Hypotonia, 800
Hypoxia, 322
Hysteria, 922
Hysterical personality, 930

I

Icterus gravis neonatorum, 738
Ictotest, 535
Idoxuridine, 105, 867
Ileitis, regional, 496
Ileus, paralytic, 501
Illusions, 917
Immediate hypersensitivity, 28, 29
Immune complex reaction, 28, 33
Immune reactions, 28-38
  and liver disease, 556
  in asthma, 376
Immune response, mechanism of, 20
Immune system, components of, 16
Immunisation, active and passive, 58, 59
Immunity, and tuberculosis, 355
  cellular, 17
  humoral, 17
Immuno-deficiency disorders, 25
  cellular, 26
  combined, 25
  humoral, 25
  secondary, 26
  treatment, 28
Immunoglobulin structure, 23
Immunoglobulins, 22
Immunological memory, 16, 18
Immunological surveillance, 42
Immunological tolerance, 16
  defect in, 38
Immunosuppression, 40
  cancer in relation to, 41
Impotence, 673
Incontinence of urine, 808
Incubation period, 48
Indomethacin, 41
  in rheumatoid arthritis, 774
Infancy, anaemia of, 723, 733
Infantile paralysis, 867
Infantilism, pituitary, 626
Infants, berberi in, 155
Infarction, cerebral, 844
  myocardial, 269
  pulmonary, 282
Infection, clinical features of, 51
  defence against, 49
  diagnosis, 52
  prevention, 57
  sources and spread of, 45
  susceptibility to, 49
  treatment, 56
Infectious diseases, 60
Infectious mononucleosis, 745
Infective endocarditis, 263
Infective hepatitis, 546
Infertility, male, 674
Influenza, 338
Inhalers, in asthma, 378
Inheritance, autosomal, 7
  dominant, 7
  hemizygous, 8
  heterozygous, 5, 8
  homozygous, 5, 8
  intermediate, 8
  multifactorial, 9
  recessive, 7
  sex-linked, 8
Insomnia, treatment of, 942
Insulin, antagonists, 677, 678
  depot, 692
  globin, 694
  isophane (NPH), 694
  lente, 693
  protamine zinc, 693
  reactions to, 697
  resistance to, 648
  semilente, 693
  soluble, 692
  ultralente, 693
  zinc suspensions, 693
Insulin induced hypoglycaemia, 664
Intention tremor, 800
Intermediate inheritance, 8
Intermittent claudication, 301
International System of Units, 1008
Intersex, 674
Interstitial lung disease, 407
Intestine, large, diseases of, 508
    examination of, 508
    tumours of, 517, 519
  small, diseases of, 488

ssusception, 502
ne, deficient intake of, 128, 647
deoxyuridine (IDU), 105
sing radiation and chromosome damage, 12
, dietary sources of, 127
  n anaemia, 725
  n rheumatoid arthritis, 776
  netabolism of, 716
  arenteral, 726
  poisoning, 959
n-dextran complex, 726
n-sorbitol, 726
ritable bowel syndrome, 525
chaemia, of bowel, 522
  renal, 616
chaemic heart disease, 265
  prevention of, 272
schio-rectal abscess, 365
slet-cell tumours of pancreas, 487
soniazid, 366
sophane (NPH) insulin, 694
soprenaline, 40
Isotope scan, cerebral, 836
  of liver, 538

J

Jacksonian epilepsy, 829
Jaundice, 538
  haemolytic, 539
  hepatocellular, 540
  obstructive, 540
Jejunal ulcer, 471
Joints, diseases of, 768
Jugular venous pressure, 209
Juxtaglomerular apparatus, 579, 582

K

Kahn test, 82
Kala azar, 962, 974
Kanamycin, 102
Karyotype, 3
Kayser-Fleischer ring, 877
Keratodermia blennorrhagica, 771
Keratomalacia, 134
Keratosis, follicular, 135
Kernicterus, 879
Kernig's sign, 856
Keto-acidosis, diabetic, 698
Ketone bodies, detection in urine, 683
Ketosis, 204
Ketostix, 683
Kidneys. *See* also Renal
  function, 579
  polycystic disease of, 617
Kidneys—*continued*
  structure, 579
  tumours of, 617
Killer (K) cells, 36
Kimmelstiel-Wilson bodies, 704
Kinins, plasma, 31
Klebsiella pneumonia, 345
Klinefelter's syndrome, 11
Koilonychia, 722
Koplik's spots, 85
Korsakoff's psychosis, 896
Kuru, 864
Kveim test, 410
Kwashiorkor, 118
Kyphoscoliosis, thoracic, 425

L

Labyrinthitis, 823
Lactosuria, 683
Lange colloidal gold curve, 853
Laryngeal obstruction, 385
Laryngeal paralysis, 312, 384
Laryngeal spasm, 385
Laryngitis, 339
  chronic, 383
Laryngoscopy, 328
Laryngo-tracheo bronchitis, 336
Larynx, 312
Lasègue's sign, 893
Latex test, 33, 772
Lathyrism, 169
LATS (long-acting thyroid stimulator), 632
LDA cytoxicity, 36
LE cells, 781
Lead poisoning, 902
Leishmaniasis, 974
Leprosy, 963, 974
Leptospirosis, 82
Leucocytosis, 719
Leucoencephalopathy, progressive, multifocal, 898
Leuco-erythroblastic anaemia, 720
Leucopenia, 719
Leukaemia, 747
  acute, 748
  aleukaemic, 747
  chemotherapy in, 749, 751, 752
  chronic lymphatic, 751
  chronic myeloid, 12, 750
  monocytic, 748
  subleukaemic, 747
Leukoplakia, of the tongue, 446
  vulvae, 675
Levodopa, 875
Lightning pains, 862
Lignocaine, 235
Lincomycin, 101

Lipid metabolism, of liver, 530
Lipoid storage diseases, 756
Liquorice derivatives, 463
Lithium carbonate, 945
Liver, acute parenchymal diseases of, 544
  acute yellow atrophy of, 549
  anatomy, 529
  biliary cirrhosis of, 561
  biopsy of, 538
  carcinoma, 568
  chronic parenchymal disease, 554
  cirrhosis of, 558
    treatment, 563
  congenital fibrosis of, 567
  detoxication of drugs, 531
  diffuse hepatic fibrosis, 558
  diseases, auto-immunity in, 38, 537
  function tests, 533
  growths of, 568
  immune reactions in, 556
  infiltrations of, 557
  metabolic activities, 530
  necrosis of, 549
  post-necrotic scarring, 561
Loa loa, 977
Lobar pneumonia, 341
Lobular pneumonia, 347
Lockjaw, 76
Löffler's syndrome, 381
Long-acting thyroid stimulator (LATS), 36
Looser's zones, 143
Lower motor neurone, 797
  lesions of, 798
Lumbago-sciatic syndrome, 892
Lung. *See* also Pulmonary
  diffusing capacity of, 320
  occupational disease of, 410
Lupus erythematosus, systemic, 35, 780
Lupus pernio, 410
Lymphadenoma, 753
Lymphoblasts, 20, 717
Lymphocytes, 717
Lymphoid cells, 36
Lymphokines, 37
Lymphoma, giant follicular, 753
  malignant, 753
Lympho-proliferative disorders, 28
Lymphosarcoma, 753
Lysergic acid (LSD), 933
Lysine-vasopressin test, 666

M

'Machinery' murmur, 291
Macroglobulinaemia, Waldenstrom's, 28
Macrophage, 20
Magnesium deficiency, 193
Magnesium intoxication, 193
Malabsorption syndrome, 488
  absorption tests, 488
  anaemia in, 727, 728, 731
  causes of, 490
  treatment, 495
Malaria, diagnosis, 967
  due to *P. falciparum* infection, 965
  due to *P. malariae* infection, 966
  due to *P. ovale* infection, 964
  due to *P. vivax* infection, 965
  parasites of, 964
  prophylaxis, 969
  protection against, 970
  radical cure of, 968
  treatment, 967
    of complicated falciparum infection,
Malignant hypertension, 277
Malignant pleural effusion, 417
Malnutrition, 112
Malta fever, 78
Maltworker's lung, 383, 411
Manic-depressive psychosis, 945
Mantoux test, 360
Maple bark disease, 383
Marasmus, nutritional, 123
Marfan's syndrome, 303
Mast cells, and IgE, 29
M.C. mask, 331
Mean corpuscular haemoglobin concentratio
    (MCHC), 719
Measles, 84
Mediastinum, tumours of, 405
Megacolon, 520
Megaloblast, 727
Meiosis, 1
Melaena, 465
  neonatorum, 765
Melphalan, in myelomatosis, 756
Ménière's syndrome, 823
Meningioma, 832
Meningism, 855
Meningitis, 855
  acute pyogenic, 857
  benign lymphocytic, 859
  meningococcal, 856
    sulphonamide in prophylaxis of, 94
  syphilitic, 861
  tuberculous, 857
  viral, 859
Meningococcal septicaemia, 856
Menopause, disorders of, 674
Mental disorders, classification of, 911
Mental state, examination of, 916
Mental subnormality, 912
Meralgia paraesthetica, 900
Mercaptopurine, 749
Mesenteric lymphadenitis, non-specific, 506
Mesenteric thrombosis, 521
Mesothelioma, pleural, 417

ssenger-RNA, 5
taphase, 2
tformin, 692
thacycline, 100
thaemoglobinaemia, 95
ethimazole, 637
ethisazone, 92, 105
ethotrexate, 40, 749
ethyl cellulose, 182
ethyldopa, 38, 279
ethysergide, in migraine, 841
etronidazole, 104, 972
etyrapone test, 665
icturition, control of, 808
Migraine, 840
Migration inhibition factor, 20
Migration inhibition test, 36
Miliary tuberculosis, 357, 361
Mineralocorticoids, 654
Minerals, 126
Miner's nystagmus, 818
Mitosis, 1
Mitral regurgitation, 253
Mitral stenosis, 254
  surgical treatment, 255
Mitral valve disease, 253
Mollusca fibrosa, 886
Mönckeberg's sclerosis, 300
Mongol, age dependent, 12
  translocation, 12
Moniliasis, complicating chemotherapy, 100
Monoamine oxidase inhibitors, 945
Monocytes, 717
Monocytosis, 720
Mononeuritis multiplex, 900
Mononeuropathy, 899
Monosomic cells, 10
Monospot test, 746
Mood, assessment of, 916
Moon-face, 656
Morphine, in pulmonary oedema, 251
Morphine addiction, 933
Motility of gastrointestinal tract, 429
  studies of, 442
Motor neurone, alpha, 797
  gamma, 797
  disease, 881
Motor pathways, 795
Motor system, 793
Mouth, diseases of, 443
  nutritional disorders of, 162, 170
Movement, involuntary, 799
Mucous patches, 81
Mucoviscidosis, 351
Multifactorial inheritance, 9
Multiple myeloma, 755
Multiple sclerosis, 869
Mumps, 87
Murmurs, cardiac, 212
Muscular dystrophy, 906
Mushroom worker's lung, 383, 411
Mustine, 755
Mutation, gene, 6
Mutism, akinetic, 827
Myalgia, epidemic, 788
Myasthenia, carcinomatous, 898
Myasthenia gravis, 37, 41, 904
Mycetoma, 372
Mycobacteria, 355
Mycoplasma infections, of respiratory tract, 337
Mycoplasma pneumoniae, 346
  tetracyline for, 100
Mycoses, pulmonary, 372
Myelofibrosis, 720
Myelography, 888
Myeloma, and immunoglobulins, 28
Myelomatosis, 755
Myeloproliferative disorders, 743
Myocardial infarction, 269
  ECG changes in, 220
Myocarditis, acute, 285
Myopathy, 898, 906
  congenital, 908
  metabolic, 908
Myositis, 908
  carcinomatous, 898
Myotonia, atrophica, 907
  congenita, 907
Myxoedema, 643
  coma, 645
  pretibial, 633
Myxoedematous madness, 643

N

Nalidixic acid, 103
Narcolepsy, 831
Nasal catheters, for oxygen, 332
Natamycin, 104
Nausea, 433
Necator americanus, 976
Necrosis, acute tubular, 609
  hepatic, 549
Necrotising papillitis, 603
Nelson's syndrome, 625, 657
Nematodes, 978
Neomycin, 102
Neostigmine, 904
Nephritis, acute, 589
  chronic, 597
  focal, 592
  glomerulo-. *See* Glomerulonephritis
  salt-losing, 599
Nephroblastoma, 618
Nephrocalcinosis, 613
Nephropathy, and antibiotics, 600

Nephropathy—*continued*
  diabetic, 704
  phenacetin, 620
Nephrotic syndrome, 595
Nerves, cranial, first, 813
    second, 814
    third, 815
    fourth, 815
    fifth, 819
    sixth, 816
    seventh, 820
    eighth, 822
    ninth to twelfth, 824
Neuralgia, trigeminal, 819
Neuralgic amyotrophy, 900
Neuritis, brachial, 900
  optic, 815
  retrobulbar, in multiple sclerosis, 870
Neurofibromatosis, 886
Neuroma, acoustic, 822
Neuromyelitis optica, 872
Neuropathy, carcinomatous, 898
  diabetic, 706
  hypertrophic interstitial, 901
  nutritional, 167
  vitamin B_{12}, 894
Neurosis, 918
  cardiac, 298
Neurosyphilis, 860
Neutropenia, cyclical, 745
Niacin, 158
Niclosamide, in tapeworm infections, 982
Nicotinamide, 158
Nicotinic acid, 158
Niemann-Pick's disease, 756
Night blindness, 133
Nitrazepam, 943
Nitrofurantoin, 103
Nitrogen mustards, 749
Non-disjunction of chromosomes, 12
Noradrenaline, 671
Nuclear sex chromatin, 4
Nutrients, energy-yielding, 116
Nutrition, qualitative aspects of, 116
Nutritional amblyopia, 169
Nutritional anaemia, 165
  in tropical countries, 166
Nutritional deficiencies, prevention, 172
Nutritional disorders, aetiology and definition, 112
  of the eyes, 133
  of the hair, 119, 170
  of the mouth, 162, 170
  of the nails, 170
  of the skin, 119, 170
Nutritional neurological syndromes, 166, 894
Nystagmus, 816
Nystatin, 104

O

Obesity, 172-183
  complications, 176
  in Cushing's disease, 656
  prevention of, 183
  treatment, 177
Obsessional personality, 928
Obsessive-compulsive neurosis, 926
Obstruction, intestinal, 501
Obstructive airway disease, 387
Occipital lobe, signs of lesion, 809
Occupational lung diseases, 410
Oculogyric crisis, 875
Oculomotor nerve, 815
Oedema, famine, 114
  production of, 194
  treatment of, 195
Oesophagitis, reflux, 449
Oesophagoscopy, 439
Oesophagus, carcinoma of, 454
  diseases of, 447
  motility of, 442
  varices of, 558
    bleeding from, 564
Oestrogen, 675
Olfactory nerve, 813
Oligospermia, 674
Oliguria, 583
Opening snap, 211
Ophthalmia neonatorum, 79
Ophthalmoplegia, 641
Opiate poisoning, 954
Optic atrophy, 815
Optic nerve, 814
Optic neuritis, 815
Optic tracts, 811
Oral hypoglycaemic drugs, 691
Orchitis, in mumps, 87
Ornithosis, 346
Orthostatic proteinuria, 586
Oscillometry, 301
Osler's nodes, 264
Osteitis deformans, 791
Osteitis fibrosa cystica, 649
Osteitis fibrosa generalisata, 649
Osteoarthrosis, 786
Osteomalacia, 142
Osteomyelitis, 790
Osteoporosis, 144
Otitis media, and cerebral abscess, 853
Ovarian failure, autoimmune, 38
Oxprenolol, 235
Oxygen therapy, 330
  adverse effects, 331
  masks, 331
  tent, 332
Oxytocin, 623

P

ave, 216
hymeningitis, hypertrophic, 861
get's disease of bone, 791
n, in chest, 268, 269, 270
leural, 321
  treatment of, 334
ncreas, anatomy and physiology, 480
carcinoma, 486
investigation, 480
islet-cell tumours, 487
radiology of, 480
ancreatic cysts, 486
ancreatic function tests, 442, 481
ancreatitis, acute, 481
  chronic, 484
Pancytopenia, 734
Panencephalitis, subacute sclerosing, 866
Papillitis, 815
Papilloedema, 814, 834
  in hypertension, 277
Papilloma of bladder, 618
Paracentesis, in ascites, 564
  in pericardial effusion, 288
Paracetamol, in rheumatoid arthritis, 774
Paracetamol poisoning, 955
Paraffin poisoning, 955
Paragonimus westermani, 977
Paralysis, agitans, 873
  bulbar, 882
  facial, 821
  general, of the insane, 861
  laryngeal, 384
  of radial nerve, 899
  of ulnar nerve, 899
  respiratory, 867
Paraplegia, 889
  spastic (lathyrism), 169
Paraproteinaemia, 755
Parathyroid glands, anatomy and physiology, 648
Paratyphoid fever, 70
Parietal lobe, signs of lesion of, 809
Parkinsonism, 873
Parotitis, 87, 447
Paroxysmal nocturnal dyspnoea, 245, 251
Paroxysmal haemoglobinuria, 740
Paroxysmal tachycardia, 231
PAS, 366
Past-pointing, 800
Patent ductus arteriosus, 291
Paul-Bunnell test, 746
PCM, classification of, 117
$P\text{CO}_2$, 317
Peak expiratory flow rate (PEFR), 329
Pectus carinatum, 425
Pectus excavatum, 425
Pel-Ebstein fever, 754
Pellagra, 158
Pendred's syndrome, 646
Penicillamine, in rheumatoid arthritis, 774
  in Wilson's disease, 877
Penicillin, 95
  adverse effects of, 98
Penicillin V, 97
Pentagastrin test, 441
Pentosuria, 683
Peptic ulcer, acute perforation, 467
  aetiology, 455
  recurrent, 471
  surgical treatment, 463
    complications of, 470
Perceptual rivalry, 806
Perforation of peptic ulcer, 467
Perfusion, of lungs, 319
Pericardial effusion, 288
Pericarditis, 287
  constrictive, 289
Perinephric abscess, 602
Peripheral circulatory failure, 251
Peripheral vascular disease, 300
Peritoneal dialysis, 611
Peritoneoscopy, in liver disease, 538
Peritonitis, 504
  tuberculous, 506
Pernicious anaemia, 728
Peroneal muscular atrophy, 901
Personality disorders, 911, 927
Pertussis, 64
Petit mal epilepsy, 828
Petroleum poisoning, 955
pH of blood, 198
Phaeochromocytoma, 671
Pharyngeal pouch, 452
Pharyngo-conjunctival fever, 336
Phenacetin nephropathy, 620
Phenformin, 692
Phenolphthalein, in urine, 588
Phenothiazine compounds, in psychiatric disorders, 943
Phenoxymethylpenicillin, 97
Phenylbutazone, 41
  agranulocytosis from, 744
  in gout, 785
  in rheumatoid arthritis, 774
Phenylketonuria, 7, 13, 908
Phenytoin, 235
Philadelphia chromosome, 12, 751
Phlebothrombosis, 307
Phobias, 919, 926
Phonocardiography, 224
Phosphatase, alkaline, 138, 534
Phosphorus, 127
Phosphorous poisoning, 955
Phrenic nerve interruption, by tumours, 403
Phrynoderma, 135
Phthalysulphathiazole, 94

Physical signs, in chest, 326
Phytohaemagglutinin, 20
Phytomenadione, 765
Pigeon chest, 425
Piperazine, treatment of threadworms, 978
Pituitary gland, anatomy and physiology, 622
  diagnosis, 623
  hormones of, 622
  tumours of, 624
Plague, 963, 974
Plasma cells, 21, 717
Platelet formation, 717
  in blood coagulation, 757
Pleura, tumours of, 418
Pleural effusion, 414
Pleural fluid, examination of, 327
Pleural pain, 321
Pleural rub, 325
Pleurisy, diaphragmatic, 321
  fibrinous, 414
Pleurodynia, 414
Plummer-Vinson syndrome, 449
Pneumococcal pneumonia, 341
Pneumoconiosis, 410
Pneumoencephalography, 836
Pneumonia, acute lobar, 341
  acute lobular, 347
  aspiration, 346
  bacterial, 341
  due to small bacteria, 345
  Friedländer's, 345
  hypostatic, 348
  Klebsiellar, 345
  pneumococcal, 341
  post-operative, 349
  staphylococcal, 344
  suppurative, 349
  treatment, 352
  tuberculous, 345
  viral, 345
Pneumothorax, spontaneous, 421
Po_2, 317
Poikilocytosis, 719
Poisoning, acute, 947
    in children, 959
  classification, 948
  therapeutic measures, 950
Poisons Information Service, 949
Polar bodies, 1
Poliomyelitis, acute anterior, 867
Polyarteritis, 305
  and asthma, 382
  and kidney, 592
  mononeuritis in, 903
Polychromasia, 719
Polycystic disease of kidneys, 617
Polycythaemia, 742
Polydipsia, hysterical, 629
Polyene antibiotics, 104
Polymask, 331
Polymyalgia rheumatica, 782
Polymyositis, 782
Polymyxin, 103
Polyneuritis, acute infective, 902
Polyneuropathy, causes of, 901
  nutritional, 167
Polyposis, multiple, of colon, 520
Polyuria, 584
Porphyria, intermittent, 588
Porphyrinuric neuropathy, 902
Portal hypertension, 558
Post-cibal syndrome, 472
Post-myocardial infarction syndrome, 289
Post-operative pneumonia, 349
Post-pneumonic effusion, 417
Postural coughing, 333
Postural hypotension, 241
Postural proteinuria, 586
Potassium depletion, 189
Potassium excess, 191
Potassium perchlorate, 638
Practolol, 235
Prausnitz-Kustner reaction, 31
Precentral lobe, signs of lesion, 809
Precocity, sexual, 663
Prednisolone, in bronchial asthma, 379
  in leukaemia, 749
  in rheumatic fever, 263
  in rheumatoid arthritis, 774
  uses and side effects of, 669
Prefrontal lobe, signs of lesions of, 808
Pregnancy, anaemia in, 724, 732
  and diabetes, 707
  heart disease in, 297
  hypochromic anaemia in, 724
  immunology in relation to, 23
  malaria in, 967
  megaloblastic anaemia in, 732
  pulmonary tuberculosis in, 357
Prevention, of blood disorders, 766
  of cardiovascular diseases, 310
  of connective tissue disorders, 791
  of diabetes, 710
  of digestive disorders, 527
  of infectious disease, 57
  of kidney and urinary diseases, 619
  of liver and biliary diseases, 577
  of nervous system diseases, 908
  of respiratory diseases, 425
  of tuberculosis, 370
Primaquine, in malaria, 969
Probenecid, 96
  in gout, 785
Procainamide, 233
Procaine benzylpenicillin, 96
Proctitis, 509
Proctoscopy, 440
Progressive bulbar palsy, 881

essive muscular atrophy, 881
ressive muscular dystrophy, 906
uanil, in malaria, 968
hase, 2
ranolol, 235
r angina, 269
hypertension, 280
state gland, benign enlargment of, 619
arcinoma of, 618
statitis, 605
tamine zinc insulin (PZI), 693
tein-bound iodine (PBI), 633
tein-calorie malnutrition, 117
otein-energy malnutrition, 117
otein deficiency, 116
otein losing enteropathy, 489
otein metabolism, in liver, 530
oteinuria, 586
  postural, 586
othrombin, in blood coagulation, 757
rothrombin time, one stage, 765
rovitamins, 131
ruritus, in jaundice, 566
  vulvae, in diabetes mellitus, 681, 705
Ps. aeruginosa infections, 98, 102
Pseudo bulbar palsy, 882
Pseudogout, 786
Pseudo hypertrophic muscular dystrophy, 906
Psittacosis, 346
Psoriatic arthritis, 771
Psychiatric assessment, in poisoning, 953
Psychiatric examination, 913
Psychogenic disorders, of digestive system, 522
Psychogenic headache, 839
Psychoneuroses, 911, 918
  cardiac, 298
Psychopathy, 930
Psychosis, 911, 939
  Korsakoff's, 896
  organic, 939
Psychosomatic disorders, 911, 935
Psychotherapy, 921
Psychotrophic drugs, uses and misuses, 942
Pulmonary abscess, 349
Pulmonary collapse, 397
Pulmonary congestion, radiological features of, 223
Pulmonary embolism, 282
Pulmonary emphysema, 390
Pulmonary eosinophilia, 381
Pulmonary fibrosis, 408
Pulmonary function, tests of, 328
Pulmonary haemosiderosis, 408
Pulmonary heart disease, 284
Pulmonary hypertension, 281
Pulmonary infarction, 282
Pulmonary lymphatic carcinomatosis, 405
Pulmonary oedema, 245, 251
Pulmonary stenosis, congenital, 294
Pulmonary tuberculosis, complications, 365
  post-primary, 362
  primary, 359
Pulmonary valve disease, 258
Pulse, 208
  alternans, 208
  anacrotic, 208
  bigeminus (coupled rhythm), 227
  bisferiens, 209
  collapsing, 208
  dicrotic, 208
  paradoxus, 209
  peripheral, 209, 301
  pressure, 214
Pulsus paradoxus, 209
Punctate basophilia, 719
Pupils, abnormalities of, 815
Purpura, 759
  anaphylactoid, 759
  Henoch Schönlein, 760
  idiopathic thrombocytopenic, 761
  senile, 760
  simplex, 759
Pyaemia, 49
Pyelonephritis, acute, 601
  chronic, 603
Pyloric stenosis, 468
Pyloroplasty, 464
Pyogenic arthritis, 771
Pyonephrosis, 613
Pyopneumothorax, 420
Pyramidal tract, lesions of, 795
Pyrexia, 51
  of unknown origin, 54
Pyridoxine, 163
Pyrimethamine, in malaria, 968
Pyruvic acid, in beriberi, 156
Pyuria, 588

Q

Q-fever, 346
QRS complex, 218
Queckenstedt's test, 852
Quinidine, 233
Quinine, in malaria, 968

R

Rabies, 972
Radiculopathy, 900
Radioactive iodine, 639
  uptake, 634
Radioactive phosphorus, in polycythaemia, 744
Radiological examination, of the chest, 327

Radiological examination—*continued*
  of digestive system, 436-438
  of heart, 223
  tumours of brain, 835-836
Radiotherapy, in ankylosing spondylitis, 780
  in bronchial carcinoma, 404
  in leukaemia, 751
  in lymphadenoma, 755
Rauwolfia, 280
Raynaud's phenomenon, 306
Reagin, 25, 29
Rebound phenomenon, 801
Rectum, carcinoma of, 517
  nervous control of, 808
Red blood cell, formation, 713
  fragility, in haemolytic anaemia, 737
  nucleated, 719
  values, 717
Reflex(es), 806
  corneal, 807
  superficial, 807
  tendon, 806
Regional enteritis, 496
Regurgitation, aortic, 256
  mitral, 253
  pulmonary, 258
  tricuspid, 259
Reiter's disease, 771
Relapsing fever, 975
Renal calculus, 613
Renal carcinoma, 617
Renal colic, 615
Renal cortical necrosis, 607
Renal dwarfism, 627
Renal failure, 597, 607
Renal hypertension, 616
Renal tubular acidosis, 582
Renin, 582
Reserpine, 280
Resistance to infections, 44
Resistance transfer factor, 44
Resonance, vocal, 325
Respiratory disease, investigation of, 324, 327
  treatment of, 329
Respiratory distress syndrome, 401
Respiratory failure, 323
Respiratory infections, 334
Respiratory paralysis, 867
Respiratory system, anatomy, 312
  physiology, 316
Resuscitation, emergency, 239
Reticulocyte, 713
Reticuloses, 753
Reticulum cell sarcoma, 753
Retinal vessels in hypertension, 276
Retinol, 132
Retinopathy, in diabetes mellitus, 704
  in hypertension, 276
Retrobulbar neuritis, 815
Rhesus factor, 41, 738
Rheumatic carditis, antigens in, 38
Rheumatic diseases, 768
Rheumatic fever, 259
  penicillin in prophylaxis of, 96
Rheumatic nodules, 261
Rheumatism, non-articular, 788
Rheumatoid arthritis, 768
Rheumatoid factor, 33, 772
Rhinitis, allergic, 374
Rhodopsin, 133
Rhonchi, 325
Riboflavin, 162
Ribonucleic acid, 5
Rickets, 137
  renal, 140
  secondary, in malabsorption syndrome, 14
  vitamin D resistant, 140
Rickettsial infections, 975
  of respiratory tract, 337
  tetracycline in, 100
Rifampicin, 367
  side effects of, 369
Rigidity, cog-wheel, 799
  lead-pipe, 799
Ringworm, griseofulvin in, 104
Risus sardonicus, 76
RNA, 5
Romberg's test, 805
Rose-Waaler test, 772
Rotor syndrome, 542
Roundworm, 978
Rubella, 86
Ruminations, 927
Rupture of heart wall, 270

S

St Vitus dance, 877
Salbutamol, 40, 378
Salicylate poisoning, 957
Salicylates in rheumatic fever, 262
Salivary glands, 446
Salmonella infections, 72
Salt, depletion, 186
  restriction, in heart failure, 250
    in hypertension, 279
Salt-losing nephritis, 187
Sandflies, in leishmaniasis, 974
Sandfly fever, 975
Sarcoidosis, 409
Scarlet fever, 61
Schick test, 66
Schilling test, 490
Schistosomiasis, 963, 976
  of liver, 567
Schizoid personality, 929
Schizophrenia, 938

iatica, 892
leroderma, 782
lerosis, amyotrophic lateral, 881
  disseminated (multiple), 869
  systemic, 782
otomata, 813
urvy, 149
edatives, 943
elf-poisoning, 949
eminoma, 618
emple vaccine, 973
engstaken tube, 564
Sensory discrimination, 805
Sensory inattention, 805, 809
Sensory pathways, 802
Sensory system, 801
  signs of lesions of, 803
Septal defect, atrial, 293
  ventricular, 294
Septicaemia, 49
Serotonin (5H-T), 31
Serum hepatitis, 548
Serum sickness, 34
Sex chromatin body, 4
Sex chromosomes, 4, 8, 11
Sex determination, disorders of, 674
Sex-linked inheritance, 8
Sexual deviation, 912, 934
Sexual disorders, in the male, 672
Sexual precocity, 663
Sheehan's syndrome, 628
Sheep cell test, 772
Shingles, 868
Shock, 251
  cardiogenic, 251
SI units, 1008
Sick sinus syndrome, 226
Sickle cell anaemia, 8
Sickle cell disease, 737
Sideroblastic anaemia, 164, 727
Sideropenic dysphagia, 449
Siderosis, 128, 411
Sigmoidoscopy, 440
Silicosis, 410
Sino-atrial block, 236
Sinuses, nasal, 312
Sinusitis, 335
Sjögren's syndrome, 38, 778
Skin, nutritional disorders of, 119, 170
Skin sensitivity tests, in asthma, 378
Sleep paralysis, 831
Sleeping sickness, 963, 974
Slow reacting substance-A, 31
Slow viral infections, 864
Smallpox, 89
Smoking. *See* Cigarette and Tobacco
Sociopathy, 930
Sodium and water accumulation, 194
Sodium depletion, 186
Sodium excess, 194
Sodium fusidate, 101
Spasticity, 795
Speech, 810
Spherocytosis, hereditary, 736
Spina bifida, 14
Spinal accessory nerve, 824
Spinal cord, compression of, 887, 1031
  transverse section of, 804
  tumours, 887
Spinothalamic tract, lesions of, 805
Spironolactone, 250
Splenectomy, in autoimmune haemolytic anaemia, 739
  in congenital haemolytic anaemia, 737
  in idiopathic thrombocytopenic purpura, 761
Splenomegaly, in anaemia,
  in Felty's syndrome, 778
  in infections, 264, 746, 965
  in leukaemia, 749, 750, 752
  in polycythaemia, 743
  in portal hypertension, 558, 756
  in reticulosis, 753
Splenovenography, 559
Splinter haemorrhages, 264
Spondylitis, ankylosing, 779
Spondylosis, cervical, 890
Sprue, tropical, 731, 732
Sputum, 320
  examination of, 327
Squint, concomitant, 816
  paralytic, 816
S-T segment, 221
Stannosis, 411
Staphylococcal infections, 63
Starvation, 114
Status asthmaticus, 379
Status epilepticus, 831
Steatorrhoea, 481, 488, 492
Stenosis, aortic, 257
  mitral, 254
  pulmonary, 258
  tricuspid, 259
Sterilisation, in haemophilia, 764
Stevens-Johnson syndrome, 95
Still's disease, 778
Stomach, aspiration of, 469
  carcinoma of, 476
  investigation of, 436-442
  peptic ulcer of, 455
  physiology of, 429
Stomatitis, 444
  angular, 162
Stool, examination of, 443
Strabismus, 816
Streptococcal infections, 61
  penicillin in, 96
Streptomycin, 102, 366

Stress disorders, 935
Stridor, 322
'Strokes', 843, 844, 845, 846
Strongyloides stercoralis, 976
Subacute combined degeneration of the cord, 894
Subarachnoid haemorrhage, 849
Subphrenic abscess, 505
Suicide, 942, 949
Sulfoxine, in malaria, 968
Sulphadiazine, 94
Sulphadimidine, 94
Sulphasalazine, 513
Sulphonamides, 94
  adverse effects of, 95
Sulphonylurea, 691
Sulphur, dietary sources of, 130
Surgery, in arthritis, 777
  in diabetes, 708
  in peptic ulcer, 463, 467, 468, 470
  in thyrotoxicosis, 638
  in ulcerative colitis, 514
Sydenham's chorea, 261, 877
Sympathetic blocking drugs, 279
Syncope, causes, 241
Synovial fluid, examination of, 772
Syphilis, 80
  of aorta, 304
  of liver, 567
  of nervous system, 860
Syringobulbia, 885
Syringomyelia, 885
Systemic lupus erythematosus, 35, 780
Systemic sclerosis, 782
Systolic murmur, differential diagnosis of, 254

T

T wave, 221
T_3, resin uptake, 634
  suppression test, 635
  thyrotoxicosis, 636
T.A.B. vaccine, 71
Tabes dorsalis, 862
Tachycardia, atrial, 231
  paroxysmal, 231
  sinus, 226
  ventricular, 231
Taenia echinocous, 983
Taenia saginata, 981
Taenia solium, 982
Takayashu's syndrome, 306
Tapeworms, 981
Taste, 820, 824
Teeth, diseases of, 443
Telangiectasia, hereditary haemorrhagic, 760
Telophase, 2
Temporal lobe, signs of lesion, 810
Temporal lobe epilepsy, 829
Tension pneumothorax, 422
Terbutaline, 378
Testis, involvement in mumps, 87
  tumours of, 618
Testosterone in hypogonadism, 673
Tests, of adrenal function, 663
  of cardiac function, 223
  of gall-bladder function, 569
  of gastric secretion, 441
  of intestinal absorption, 488
  of liver function, 533
  of mental state, 916
  of oesophageal function, 437, 439, 442
  of pancreatic function, 442
  of pituitary function, 623
  of pulmonary function, 328
  of renal function, 585
  of thyroid function, 633
Tetanus, 76
  local, 77
Tetany, 652
  in rickets, 138
Tetracyclines, 100
Tetralogy of Fallot, 295
Thalassaemia, 8, 15, 737
Thiabendazole, in trichinosis, 981
Thiacetazone, 366
Thiamin, 152
Thiodiazine diuretics, 195, 249
Thioguanine, in leukaemia, 749
Thiouracil, 638
Thomsen's disease, 907
Thoracic outlet compression syndrome, 900
Thoracoscopy, 328
Thought processes, assessment of, 917
Threadworm, 978
Thrills, cardiac, 211
Thrombo-angiitis obliterans, 305
Thrombocythaemia, haemorrhagic, 766
Thrombocytopenia, 720
Thrombocytosis, 766
Thrombophlebitis, 307
  suppurative, 308
Thromboplastin, in blood coagulation, 757
Thrombosis, cavernous sinus, 851
  cerebral, arterial, 844
    venous, 851
  coronary, 267
  of posterior inferior cerebellar artery, 844
  of renal vein, 596
  venous, 307
Thrombotest, 765
Thrush, 67, 372
Thymectomy, 17, 18, 41
Thymic hypoplasia, 27
Thymus gland, 16
Thyroid gland, anatomy and physiology, 631
  autoimmune disease, 32

roid gland—*continued*
arcinoma, 646
roid stimulating hormone (TSH), 623
roidectomy, 638
roiditis, 645
le Quervain's 646
Hashimoto's 32, 37, 645
yrotoxic crisis, 641
yrotoxicosis, 631
neonatal, 36
yroxine (T_4), 631
effective ratio (ETR), 634
in hypothyroidism, 644
total serum, 634
c, 881
c douloureux, 819
ssue typing, 16
lymphocytes, 17-22
obacco amblyopia, 815
obramycin, 102
odd's paralysis, 829
olbutamide, 691
ongue, diseases of, 446
onsillitis, streptococcal, 67
orticollis, 880
Toxocara canis, 979
Toxoplasmosis, blood changes in, 747
Trachea, obstruction of, 386
Tracheitis, acute, 336
Tracheo-oesophageal fistula, 386
Tracheostomy, 332
Tranquillisers, 943, 944
Transaminase, in liver disease, 536
  in myocardial infarction, 269
Transfusion, blood, for shock, 252
  dextran, 253
  plasma, 253
Transketolase, in beriberi, 156
Transplantation, of organs, 16, 41
  of kidney, 600
Transplantation antigens, 16
Transvestism, 934
Trematodes (flukes), 973
Tremor, 799
Treponemal tests, 82
Triamterene, 196, 250
Trichinella spiralis, 980
Trichuris trichiura, 980
Tricuspid valve disease, 258
Tricyclic antidepressants, 945
  poisoning by, 957
Trigeminal nerve, 819
Trigeminal neuralgia, 819
Triiodothyronine (T_3), 631
Triiodothyronine (T_3) resin uptake, 634
Trinitrin, 269
Triple rhythm, 212
Trisomic cells, 10
Trochlear nerve, 815
Trophic lesions, in syringomyelia, 885
Tropical ataxic neuropathy, 168
Tropical pulmonary eosinophilia, 381
Tropical sprue, 731, 732
Trousseau's sign, 653
Trypanosomiasis, 963, 974
Tsetse flies, 963
TSH, in thyroid disease, 636
Tubercle bacilli, resistant, 369
Tuberculin test, 360
Tuberculosis, 354
  acute miliary, 361
  chemotherapy, side effects of, 368
  clinical features, 358
  diagnosis, 364
  of bone, 790
  of kidney, 606
  pathology, 357
  pneumonic, 363
  prevention, 370
  primary pulmonary, 359
    in diabetics, 705
    post-primary, 362
  symptomatic treatment, 370
  treatment, 366
    inexpensive regimens, 368
Tuberculous arthritis, 771
Tuberculous empyema, 419
Tuberculous enteritis, 365
Tuberculous infection, primary, 359
Tuberculous meningitis, 857
Tuberculous pericarditis, 288
Tuberculous pleural effusion, 416
Tuberculous pneumonia, 345
Tubular function, defects of, 582
Tubular necrosis, 607, 609
Tumours. *See* under each organ.
Turner's syndrome, 11
Typhoid fever, 69
Typhus fevers, 962, 975

U

Ulcer, jejunal, 471
  peptic. *See* Peptic ulcer
Ulcerative colitis, 508
  antigens in, 38
Ulcerative stomatitis, 444
Ultrasound, in arterial disease, 301
Undernutrition, 114
Undulant fever, 78
Unipolar leads, 215
Upper motor neurone, 794
  lesions of, 796
Uraemia, 597, 607
Urethral syndrome, 605
Urethritis, 605
  gonococcal, 79

Urethritis—*continued*
  non-gonococcal, 80
Uric acid, in gout, 784
Uricosuric agents, 785
Urinary tract, infection, 601
    in diabetes, 705
  obstruction of, 612
  tumours of, 617
Urine, abnormal constituents, 586-589
  reaction, 585
  specific gravity of, 584
  volume of, 583
Urobilinogen, urinary, in haemolytic anaemia, 736
    in liver disease, 536
Urticaria, 30

V

Vaccination (B.C.G.)
  in rabies, 973
  measles, 85
  smallpox, 92
  T.A.B., 71
  yellow fever, 975
Vaccination schedule, 59
Vaginitis, senile, 675
Vagotomy, 464
Vagus nerve, 824
Valvotomy, in aortic stenosis, 258
  in mitral stenosis, 255
Valvular disease of the heart, 253
Varices, of oesophagus, 558
  bleeding from, 564
Variola, 89
Variola minor, 89
Vascular disorders, in diabetes, 703
Vasoconstrictors, for shock, 252
Vasopressin, 630
  in bleeding from oesophageal varices, 564
Vasovagal attacks, 241
V.D.R.L., 82
Veins, diseases of, 307
Vena cava, obstruction of, 406
Venereal disease, 79-82
Venesection in heart failure, 251
Venous thrombosis, 307
Ventilation, 317
  assisted, 332
Ventilation/perfusion ratio, 319
Ventilatory capacity, estimation of, 328
Ventilatory failure, 323
  treatment of, 332
Ventimask, 331
Ventricular fibrillation, and cardiac arrest, 240
Ventricular hypertrophy, electrocardiogram in, 219
Ventricular septal defect, 294
Ventricular tachycardia, 231
Vertebro-basilar thrombosis, 844
Vertigo, 823
Vestibular nerve, disorders of, 823
Villous atrophy, 493
Vinblastine, 755
Vincent's angina, 67, 444
Vincristine, 749
Viper venom, in control of bleeding, 763
Viral diseases of respiratory system, 337
Viral hepatitis, 545
Viral infections, immunity in relation to,
Viral meningitis, 859
Viral pericarditis, 288
Virilisation, 663
Virus infections, of respiratory tract, 337
Visual pathway, 811
  signs of lesions of, 812
Vitamin A, 132
Vitamin B_1, 152
Vitamin B_6, 163
Vitamin B_{12}, 164, 715, 727, 730
  absorption of, 490
  neuropathy, 168, 894
Vitamin B complex, 182
Vitamin C, 148
Vitamin D, 135
  dangers of excessive intake of, 141
Vitamin deficiency, biochemical diagnosi
    170
  subclinical, 170
Vitamin E, 130
Vitamin K and related substances, 148
  in hypoprothrombinaemia, 765
Vitamins, biosynthesis in the gut, 131
  essential for man, 130
  recommended intakes, 131
  utilisation of, 131
Vivax malaria, 965
VMA, 672
Volvulus of intestine, 502
Vomiting, 433
  psychogenic, 524
von Gierke's disease, 557
Von Recklinghausen's disease, 649, 886
Von Willebrand's disease, 760

W

Warfarin, in venous thrombosis, 309
Wassermann reaction, 82
  false positive, in glandular fever, 746
Water and electrolytes, 126
  disturbances of, 185-188
Water depletion, 188
Water intoxication, 193
Waterbrash, 434
Waterhouse Friderichsen syndrome, 660

lkiller poisoning, 954
hts, desirable for adults, 1007
r age, birth to 5 years, 1006
's disease, 552
ckebach's phenomenon, 237
nicke's encephalopathy, 896
eze, 322
pworm, 980
te blood cell, formation, 716
lues, 717
O, and tropical disease, 961
ooping-cough, 64
lal reaction, 70
m's tumour, 618
son's disease, 876
ind', 435
oody leg' in scurvy, 149
rms, 973

X

chromosome, 4, 11
Xanthomatosis, 557
Xerophthalmia, 134
Xerosis conjunctivae, 134
Xerostomia, 447
Xylose absorption, 489

Y

Y chromosome, 4, 8
Yaws, 975
Yeast, 153
Yellow fever, 962, 975

Z

Ziehl-Neelsen stain, 364
Zinc deficiency, 130
Zollinger-Ellison syndrome, 470
Zona fasciculata/reticularis, investigation, 658
Zona glomerulosa, overactivity, 659
Zygote, 2

Printed by T. & A. Constable Ltd., Edinburgh

TROPICAL DISEASES

The Authors

FREDERICK J. WRIGHT

M.A., M.D.Cantab., F.R.C.P.Edin., F.R.C.P.Lond., D.T.M. & H.Eng.

Head of Medical Department, Kilimanjaro Christian Medical Centre, Moshi, Tanzania
Honorary Senior Lecturer in Medicine, University of Dar es Salaam, Tanzania
Formerly Senior Lecturer in Diseases of Tropical Climates, University of Edinburgh
Previously Government Medical Specialist, Kenya

SIR JAMES BAIRD

K.B.E., M.D., F.R.C.P.Edin., F.R.C.P.Lond.

Lieutenant-General, late R.A.M.C.
Director-General of Army Medical Services
Formerly Professor of Military Medicine of the Royal Army Medical College and the Royal College of Physicians, London
Previously Officer-in-charge Medical Division, British Military Hospital, Singapore

Supplement to
DAVIDSON'S PRINCIPLES AND PRACTICE OF MEDICINE
Eleventh Edition Edited by
JOHN MACLEOD

TROPICAL DISEASES

BY

FREDERICK J. WRIGHT

AND

SIR JAMES BAIRD

FIFTH EDITION

THE ENGLISH LANGUAGE BOOK SOCIETY
and
CHURCHILL LIVINGSTONE
1974

CHURCHILL LIVINGSTONE
Medical Division of Longman Group Limited

Distributed in the United States of America by Longman Inc., New York and by associated companies, branches and representatives throughout the world.

© E. & S. LIVINGSTONE LIMITED, 1964, 1967, 1968
© LONGMAN GROUP LIMITED, 1971, 1974

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, without the prior permission of the publishers (Churchill Livingstone, 23 Ravelston Terrace, Edinburgh).

First Edition	1964
Reprinted	1965
First E.L.B.S. Edition	1965
Second Edition	1967
Second E.L.B.S. Edition	1967
Third Edition	1968
Third E.L.B.S. Edition	1968
Fourth Edition	1971
Reprinted	1972
Fourth E.L.B.S. Edition	1971
Reprinted	1972
Reprinted	1972
Fifth Edition	1974
Fifth E.L.B.S. Edition	1974

Printed in Great Britain

eface to the Fifth Edition

avidson's *Principles and Practice of Medicine* has proved to be a popular xtbook in many parts of the world. However, the valid criticism was made by udents and doctors in tropical countries that it did not include a description f many diseases of common occurrence and great importance to them. For udents in temperate climates the inclusion of an account of these diseases ould add unnecessarily to the size and scope of the book. Accordingly in 1964 r Stanley Davidson decided to publish a supplement intended primarily for udents and general practitioners living in the tropics. This was very well eceived and now enters its fifth edition under the joint authorship of Dr F. J. Wright and Lieutenant-General Sir James Baird. It includes a section on naemia in the Tropics written by Dr N. C. Allan, Senior Lecturer in Haema- ology, University Department of Medicine, Western General Hospital, dinburgh and formerly of University of Ibadan, Nigeria. As no attempt has een made to cover fully all aspects of tropical medicine, advanced books on opical medicine or helminthology should be consulted for further study.

To avoid unnecessary repetition, tropical diseases described in *Davidson's rinciples and Practice of Medicine*, either because they are sometimes en- ountered in temperate climates or because they are of particular educational alue, have not been included in this supplement. These are:

moebiasis. . . .	p. 970	Leptospirosis . . .	p. 82
scariasis	p. 979	Malaria	p. 964
Bacillary dysentery . .	p. 74	Nutritional disorders . .	p. 111
Beriberi	p. 153	Pellagra	p. 158
Blackwater fever . .	p. 966	Psittacosis. . . .	p. 346
Brucellosis	p. 78	Rabies	p. 972
Cardiomyopathy (tropical) .	p. 286	Salmonelloses . . .	p. 72
Cysticercosis . . .	p. 982	Smallpox . . .	p. 89
Enteric fevers . . .	p. 69	Taeniasis	p. 981
Enterobiasis . . .	p. 978	Tetanus	p. 76
Kwashiorkor . . .	p. 118	Trichinosis . . .	p. 980

The authors are much indebted to the following for expert advice on the ubjects indicated: Drs S. G. Browne (leprosy), A. D. M. Bryceson (cutaneous eishmaniasis and relapsing fever), Mr D. P. Burkitt (Burkitt's tumour), Dr R. N. Chaudhuri (cholera), Professor L. H. Collier (trachoma), Mr J. Cook Kaposi's sarcoma) and Dr R. N. T. Thin (melioidosis).

I am grateful to Dr J. C. Gould and to the Oxford University Press for ermission to print illustrations taken from *Medicine—The Diagnosis and Treatment of Prevalent Disease* by F. J. Wright and J. C. Gould, and to the late Brigadier L. S. R. Macfarlane for illustrations taken from *Human Protozoology nd Helminthology*, published by Churchill Livingstone.

The authors also wish me to express their thanks to the many other colleag who have given help and advice and to our publishers, Churchill Livingst for their kindly assistance and invaluable guidance throughout the prepara of this book.

1974

JOHN MACLEO

ntents

PAGE

RODUCTION 1

EASES DUE TO PROTOZOA 2

Leishmaniases, Trypanosomiases, Balantidiasis, Giardiasis, Toxoplasmosis.

EASES DUE TO BACTERIA, SPIROCHAETES AND SPIRILLA 15

Granuloma venereum, Bartonellosis, Melioidosis, Leprosy, Cholera, Anthrax, Plague, Tularaemia, Chancroid, Yaws, Endemic syphilis, Pinta, Relapsing fevers, Rat-bite fevers.

SEASES DUE TO VIRUSES AND RICKETTSIAE 40

Arboviruses, Yellow fever, Dengue, Sandfly fever, Kyasanur Forest disease, Japanese B encephalitis, Lassa fever, Haemorrhagic fever with renal syndrome, Kuru, Lymphogranuloma inguinale, Trachoma, Typhus fevers, Q fever, Rickettsialpox, Trench fever.

SEASES DUE TO HELMINTHS 61

Schistosomiasis, Clonorchiasis, Paragonimiasis, Fascioliasis, Fasciolopsiasis, Ancylostomiasis, Strongyloidiasis, Larva migrans, Filariases, Dracontiasis.

ISEASES DUE TO FUNGI 88

Superficial mycoses, Histoplasmosis, Mycetoma, Notes on other mycoses.

ISCELLANEOUS CONDITIONS 96

The Chigoe flea, Porocephalosis, Myiasis, Poisonous bites, Poisonous stings, Tropical phlebitis, Tropical myositis, Fibrosis of the liver peculiar to the tropics, Tropical ulcer, Buruli ulcer, Cancrum oris, Burkitt's lymphoma, Kaposi's sarcoma, Epidemic dropsy, Vomiting sickness of Jamaica, Subacute myelo-optico neuropathy, Effects of light and heat, Tropical sprue.

NAEMIA IN THE TROPICS 124

Iron deficiency and megaloblastic anaemias, Haemolytic anaemia due to malaria, glucose-6-phosphate dehydrogenase deficiency and the haemoglobinopathies, Thalassaemia, Splenomegaly and anaemia, Onyalai.

IDEX 141

ntroduction

---

s stated in the preface to this Supplement, page v, certain important tropical iseases have already been described in *Davidson's Principles and Practice f Medicine* where some introductory comments and historical notes are also ecorded (pp. **961-984**).*

The conditions to be described here are grouped largely on an aetiological asis, beginning with further important protozoal infections. In the practice f tropical medicine it is, however, important to appreciate that an infecting gent may be only one factor in the malady produced. What transpires is often materially influenced by genetic endowment, inherited or acquired immunities, the nutritional state and the presence of concomitant diseases. Therefore it is better to think of the host-parasite relationship or the state of the patient in his environmental setting, rather than the characteristics of defined diseases. Similarly prevention and treatment are related primarily to the community or individual patient, not necessarily to the invading parasite. Nevertheless there are many specific infective agents responsible for ill-health in the tropics and, with the exception of the smaller viruses, the majority are amenable to specific chemotherapy if this can be taken to the patient. In any one locality it is prudent to learn what are the prevailing manifestations of endemic disorders. Thus the usual causes of splenomegaly, anaemia or jaundice may differ widely from place to place.

Some non-infective diseases vary greatly in their incidence in underdeveloped countries compared with affluent countries. Thus atherosclerosis, diverticular disease, carcinoma of the colon, thrombophlebitis and varicose veins are relatively rare among the indigenous races of the tropics. There are also, however, marked variations in the incidence of certain conditions, e.g. oesophageal carcinoma and duodenal ulceration between adjacent peoples. It is to be hoped that the elucidation of environmental differences, including dietary variations, will throw light on the aetiology of such diseases. In general, diseases associated with stress tend to be infrequent in the tropics. The prevalence of infective hepatitis is an indication of defective hygiene. Road accidents are becoming an increasing hazard in developing countries.

It may be noted that a few conditions, which occur only in temperate regions, have been included, e.g. rickettsialpox. This has been done to complete groups of diseases and to describe certain related conditions which have not been included in *Davidson's Principles and Practice of Medicine*.

---

* Cross references to this book are given in bold type.

Diseases due to Protozoa

LEISHMANIASES

THIS group of diseases is caused by protozoa of the genus *Leishmania*, conveyed to man by female sandflies in which the flagellate forms of leishmania are found. In man the leishmaniae are found in reticulo-endothelial cells in characteristic oval forms known as amastigotes or Leishman-Donovan (LD) bodies (Fig. 1). Leishmaniasis may take the form of a generalised infection called visceral leishmaniasis or kala azar. Localised lesions of the skin occur in cutaneous leishmaniasis or oriental sore. South American leishmaniasis may remain confined to the skin or progress to ulceration of mucous membranes. The causative leishmaniae are morphologically identical but differ in their serological reactions.

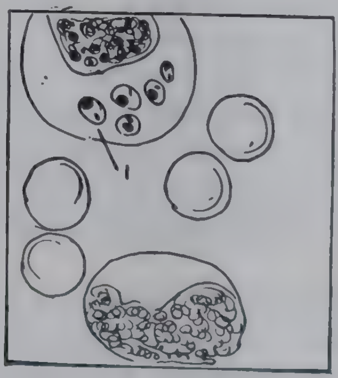


FIG. 1

1 Leishman-Donovan bodies.

Visceral Leishmaniasis

(KALA AZAR)

Kala azar is caused by *Leishmania donovani*.

Geographical Distribution. It is prevalent in the Mediterranean littoral, Ethiopia, Sudan, parts of East and West Africa, Asia Minor, mountainous regions of Southern Arabia, eastern parts of India, China and South America. In India man appears to be the chief host but in many areas, including the Mediterranean area, dogs are the main reservoir of infection. In the latter region the disease in local residents occurs chiefly in childhood, after which there is a degree of immunity.

Pathology. Multiplication, by simple fission, of leishmaniae takes place in reticulo-endothelial cells which rupture and the LD bodies are distributed to reticulo-endothelial cells in various organs, including the liver and spleen which become greatly enlarged. There is a marked progressive granulocytopenia, the leucocyte count often falling to 2,000 mm^3 or lower, and a slowly progressive anaemia. There is a great increase of gamma globulin. Successful chemotherapy reverses these changes; only rarely does appreciable fibrosis of the liver occur.

casionally after recovery a condition of post-kala azar dermal leishmaniasis velops (see below).

Clinical Features. The incubation period of visceral leishmaniasis is usually bout one or two months but exceptionally it may be prolonged for years, up 10 years having been recorded. The onset may be insidious or abrupt with eating and high intermittent fever, sometimes showing a double rise of mperature in the 24 hours. The spleen and usually also the liver to a rather ss degree soon become enlarged, the spleen, after some weeks, often reaching great size. If not treated the patient will become anaemic and wasted, frequently ith increased pigmentation especially on the face. Except in acute cases the atient may remain ambulant although febrile. Lymph nodes may be enlarged. arely lymphadenopathy is the only clinical abnormality. In India about 5 per ent of cases, one to two years after apparent cure, develop post-kala azar ermal leishmaniasis. In some other countries this condition occurs less frequently but rather sooner. It may present first as hypopigmented or eryhematous macules on any part of the body and later a nodular eruption may ppear, especially on the face. In the macular lesions scanty intracellular LD bodies may be found. In nodules they are more abundant.

Diagnosis. The somewhat variable clinical picture of visceral leishmaniasis and leucopenia are usually supported by a high level of gamma globulin demonstrable by paper electrophoresis of the blood and responsible for the positive formol-gel test. The latter is carried out by adding 1 drop of commercial formalin to 1 ml of the patient's serum. In an established case the serum becomes solid and opaque within 20 minutes. A complement-fixation test is available and an immunofluorescent test has been developed. The leishmaniae (as LD bodies) may be demonstrated by staining material obtained by puncture of sternal marrow or lymph node or, failing these, by puncture of the spleen or liver. Culture of blood or marrow aspirate on a special medium at room temperature may yield the flagellate forms of the leishmania after incubation for periods of one to three weeks. Kala azar has to be differentiated from typhoid fever and brucellosis, for the diagnosis of which agglutination tests and culture of the blood are employed, and from malaria by examination of blood films. The hepatosplenomegaly may be simulated by schistosomiasis. Tuberculosis, leukaemia and reticulosis may be incorrectly suspected. Any of these conditions, but expecially those due to endemic infections, may be present in addition to kala azar. Post-kala azar dermal leishmaniasis has to be distinguished from leprosy, yaws, syphilis, lupus vulgaris, drug sensitivity and other dermatoses.

Treatment. The response to treatment varies with the geographical area in which the disease has been acquired. In Asia the disease is readily cured, but in the Sudan and East Africa it is more resistant. Sodium stibogluconate, a pentavalent antimony compound, gives good results. A solution containing 100 mg/ml is available for intravenous or intramuscular use. A suitable course of treatment for an adult is 10 daily intravenous injections of 600 mg repeated, if necessary, after an interval of 14 days up to a total dosage of 12 or even 18 g. Children tolerate a relatively larger dose of antimony than adults and seem to require it. One-third of the adult dose may be given to children from 5 t 10 years of age.

The diamidine compounds, pentamidine isethionate employed as in trypanosomiasis (p. 9) and 2-hydroxystilbamidine isethionate, have been found usefu in some areas where the disease is resistant to treatment with antimony compounds. The dose of 2-hydroxystilbamidine for an adult is 250 mg intravenousl daily for 10 days; the course may be repeated after an interval of 14 days up tc a total of 7·5 g given over a period of 58 days. Side-effects such as fever, rigor and headache are not uncommon with this treatment but can be relieved by giving 10 mg of mepyramine maleate three times a day during the course.

The results produced in each case must be assessed and treatment continued as required. Favourable signs are absence of fever, increase in weight, improvement of the anaemia, a normal white cell count, return towards normal level of serum gamma globulin, recession of the spleen and negative lymph node puncture. For the treatment of post-kala azar dermal leishmaniasis the same drugs are used as for visceral leishmaniasis but the response is slower, and intermittent treatment for months may be required. Some respond well to pentamidine isethionate. A generous diet should be given and any concomitant disease treated.

Prophylaxis. In an endemic area infected dogs should be destroyed. Sandflies should be combated (p. 46). Treatment of human infections reduces their infectivity for sandflies.

Cutaneous Leishmaniasis

(ORIENTAL SORE)

Oriental sore, which is caused by *Leishmania tropica* is widespread in the tropics and subtropics. It is conveyed from many different animals to man by certain species of sandflies after the leishmaniae have undergone a cycle of development in these insects.

Pathology. In the early stages, before ulceration, there is a granulomatous reaction in the corium consisting of lymphocytes, plasma cells and numerous hypertrophic reticulo-endothelial cells, some of which are packed with leishmaniae. As the process extends, the epithelium becomes thinned and the raised papule ulcerates in the centre and later suffers pyogenic infection. The margin of the ulcer consists of dense epithelial proliferation and in the centre the whole thickness of the skin is destroyed. The base of the ulcer consists of granulomatous cells. Considerable scarring may result, especially where there has been marked secondary infection.

Clinical Features. The incubation period is from two weeks to five or more years but usually is from two to three months. Lesions, single or multiple on exposed parts of the body, start as small itchy red papules and with increase in size a scab forms on the surface. Untreated this will progress to form a rounded ulcer with well-defined indurated raised margins and a granulomatous base.

ese lesions may be up to 10 cm or more in diameter. A seropurulent discharge udes which may dry and form an adherent scab. Pain is not a feature and neral symptoms are usually absent. Sometimes, instead of an ulcer, a fungating dular mass develops. Occasionally leishmaniae spread from the sore and these use nodules to develop in the course of the lymphatics with enlargement of related nodes. Untreated the ulcer lasts about a year. Immunity has by then veloped and this will prevent further infection. After healing a thin depressed pigmented scar remains. Cutaneous leishmaniasis may occur in a persistent apsing form (leishmaniasis recidiva) having a tuberculoid histology.

Diffuse cutaneous leishmaniasis occurring in Ethiopia and Venezuela is obably attributable to a defective host reaction to *L. tropica*. After the itial lesion diffuse hypertrophic lesions develop and, untreated, spread exorably to involve much of the body. The lesions contain numerous LD odies engulfed by macrophages.

Diagnosis. The appearance of the lesion in a patient from an endemic area ggests the diagnosis. Leishman-Donovan bodies can be demonstrated by serting a dry needle into the margin of the ulcer or curetting the edge and aining the material obtained with Giemsa's stain or culturing it on a special edium at room temperature. A Leishmanin (Montenegro) skin test (p. 6) is ositive except in untreated diffuse cutaneous leishmaniasis. Other localised skin sions such as those of rodent ulcer, yaws, leprosy and primary syphilis have o be differentiated.

Treatment. An important part of the general treatment in long-standing ases is the cleansing of the ulcer. The crust should be removed by the application f moist dressings and the exposed surface then kept clean. In addition it may e necessary to administer an antibiotic if secondary pyogenic infection is resent.

Specific treatment to eradicate the leishmaniae is given either locally or arenterally, the choice being influenced by the number and distribution of he lesions. For only one or at the most three lesions, local treatment is often uccessful. Unipolar coagulation diathermy has replaced earlier methods of nducing an inflammatory reaction.

When the lesions are multiple it is better to treat the patient by parenteral njections of pentavalent antimony compounds such as sodium stibogluconate s prescribed for visceral leishmaniasis (p. 3), and this, combined with local leansing of the lesion, is also preferable for a solitary lesion on the face. Some esions are relatively resistant and require prolonged antimony therapy. A useful lternative is oral dehydroemetine. This is presented as the dihydrochloride or esinate. The dose is 3 to 4·5 mg/kg body weight, daily, in three divided doses, or four weeks.

Diffuse cutaneous leishmaniasis responds poorly to antimonials. Cure can sually be achieved by repeated courses of intramuscular pentamidine isethionate p. 9) but weekly glucose tolerance tests are required to detect the early signs f drug-induced diabetes. Response may also be obtained to intravenous mphotericin B (p. 90). With successful treatment the Leishmanin skin test ecomes positive and the lesions fibrose.

Prophylaxis. In addition to those preventive measures described under viscera leishmaniasis against animals and sandflies, a lasting immunity can be achieve by deliberate inoculation of a living culture of *L. tropica*. This produces a ulcer, but the site chosen for the inoculation is one normally covered by clothin so scarring does not cause undesirable disfigurement. This procedure does no protect against visceral leishmaniasis for which no effective vaccine has bee prepared.

South American Leishmaniasis

South American leishmaniasis is caused by a number of species of leishmania. e.g. *L. braziliensis*, *L. mexicana* and *L. peruviana*. They occur only in hot, moist. afforested regions and are conveyed to man from a variety of animals by several species of sandflies. The disease can be separated into three types. There is the 'espundia' of Brazil caused by *L. braziliensis*. Secondly there is the 'chicleros ulcer' or 'bay sore' attributable to *L. mexicana* found in Mexico. Guatemala and Honduras among gatherers of chicle, used for making chewing gum. The third variety is the disease occurring in the Guianas and Peru, known as 'uta' and caused by *L. peruviana*. Diffuse cutaneous leishmaniasis was atttibuted in Venezuela to a distinct species *L. americana* or *L. pifanoi*. It is probably an abnormal host reaction to *L. tropica* (p. 5).

Geographical Distribution. The infections are endemic in Central and South American countries and in parts of Mexico.

Pathology. The microscopic appearances of the skin lesions may be similar to oriental sore but are not always characteristic and diagnosis may therefore have to depend on the demonstration of the parasite, which is often difficult. The mucocutaneous lesions begin as a perivascular infiltration; later endarteritis may lead to destruction of the surrounding tissues (see below).

Clinical Features. In the classical espundia of Brazil and surrounding regions the initial papulo-pustular cutaneous lesions may be localised or widespread and affect especially the face, ears, elbows and knees. Mucosal lesions either accompany the skin lesions or appear some years later. The nasal mucosa becomes congested and later all tissues of the nose ulcerate except for the bone. The lips, soft palate and fauces may be invaded and destroyed leading to terrible suffering and deformity. Secondary bacterial infection is a common aggravating factor.

Chicleros ulcers affect mostly the ears and the lesions often last many years. They start as small painless pimples which enlarge to become larger papules going on to ulceration and erosion of the pinna. The lesions of uta rarely progress beyond the skin. They are often multiple and papillomatous rather than ulcerative.

Diagnosis. This depends on the history and clinical appearance, confirmed by demonstration of the protozoon by punch biopsy. As parasites are not easily found the Leishmanin (Montenegro) test is of value. In this an antigen pared from a culture of leishmaniae is used and 0·1 ml of this is injected radermally. A positive case will show erythema and induration at the site the injection after 48 hours. South American leishmaniasis has to be dis- guished from leprosy, yaws and various fungal diseases.

Treatment. Early cases and those exhibiting chicleros ulcers may be suc- ssfully treated by sodium stibogluconate given as recommended for visceral shmaniasis (p. 3). In more advanced cases amphotericin B, although a toxic ug, given by intravenous infusion as for histoplasmosis (p. 90) may succeed. rimethamine, given orally, has also been used successfully. Three courses, ch lasting 10 days, are given, separated by rest periods of 8 days. In the st two courses the daily dose is 50 mg; in the third it is reduced to 25 mg.

AFRICAN TRYPANOSOMIASIS

(SLEEPING SICKNESS)

African sleeping sickness is caused by trypanosomes conveyed to man by the ites of infected tsetse flies of either sex.

Geographical Distribution. The disease is acquired only in Africa between 2° N and 25° S. There are two trypanosomes which affect man, *Trypanosoma ambiense* conveyed by *Glossina palpalis* and *G. tachinoides* and *T. rhodesiense* ransmitted by *G. morsitans*, *G. pallidipes*, *G. swynnertoni* and also *G. palpalis*. Gambiense trypanosomiasis has a wide distribution in West and Central Africa eaching to Uganda and Kenya; rhodesiense trypanosomiasis is found in parts of East and Central Africa. *G. palpalis* is found only on or near the shady banks of lakes and streams; *G. tachinoides* travels farther afield. *G. swynnertoni* is imited to Tanzania and, in common with other vectors of rhodesiense sleeping sickness, flies across open country covered with scrub. In these areas wild animals are found commonly to be affected by other trypanosomes, such as *T. vivax*, *T. congolense* and *T. brucei* which also cause much sickness among cattle. These trypanosomes thus indirectly affect man by reducing greatly the grazing areas on which cattle can survive, thus reducing supplies of milk and meat, prime requirements for the prevention of protein malnutrition. *T. brucei* has not been distinguished morphologically or antigenically from *T. rhodesiense* but only the latter is pathogenic for man. Experimentally mice can be protected by human plasma against *T. brucei*, but not against *T. rhodesiense*. On epi- demiological grounds it appears that there is undoubtedly a reservoir of infection of *T. rhodesiense* in wild animals and, at times, in cattle. Experimental trans- mission of *T. rhodesiense* to man from a bushbuck has been achieved but this does not establish that this animal is the most important reservoir host. There s also evidence that at times *T. gambiense* may be harboured by cattle. It is arguable whether *T. gambiense* and *T. rhodesiense* should be regarded as different species or as divergent strains of one species.

Pathological and Clinical Features. Even during an epidemic of trypano- omiasis, only a low percentage of tsetse flies are infected. A bite by a tsetse fly is frequently painful but, if trypanosomes are introduced, the site of the bi may again become painful and swollen about 10 days later. The lesion is som times described as a 'trypanosomal chancre'. Trypanosomes can be recovere from it. Within two to three weeks of infection the trypanosomes invade th blood stream. In gambiense infections the disease usually runs a relatively slo course with irregular bouts of moderate fever and enlargement of lymphati nodes. These are characteristically firm, discrete, rubbery and painless and ar particularly prominent in the posterior triangle of the neck. Sometimes durin these early weeks transient circinate erythematous eruptions can be seen particularly on the front or back of the chest and especially if the patient ha a white skin. Bouts of fever lasting a week or more recur over a period o months and tachycardia persists in the apyrexial intervals. The spleen an liver may become palpable. Varying degrees of chronicity may be encountere and signs and symptoms may be few. After some months, in the absence o treatment, the central nervous system is invaded. This is shown clinically b headaches and changed behaviour, insomnia by night and sleepiness by day, mental confusion and eventually tremors, pareses, wasting from inanition, coma and death. The earliest sign of invasion of the nervous system is an increase of protein and cells in the cerebrospinal fluid. The histological changes in the brain are similar to those found in viral encephalitis but trypanosomes are scattered in the substance of the brain and large eosinophilic mononuclear cells with a deeply stained oval eccentric nucleus (morula cells) are a feature. Sometimes gambiense infections run a more acute course resembling the illness more typical of rhodesiense trypanosomiasis.

In rhodesiense infections enlargement of the lymph nodes is not a prominent feature. Fever is higher and more constant than in gambiense infections, so that within a few weeks the patient is severely ill and may have developed pleural effusions and signs of myocarditis or hepatitis. The clinical manifestations of involvement of the nervous system may not be obvious but within a few weeks of infection the cerebrospinal fluid will be abnormal and in the untreated case death ensues from toxaemia or heart failure, often with complicating factors such as pneumonia or dysentery. If the illness is a little less acute, tremors, drowsiness and coma may develop.

Diagnosis. In any febrile patient from an endemic area trypanosomiasis should be considered. In rhodesiense infections the trypanosomes can usually be detected by microscopic examination of a wet blood film. Agitation of red cells by the trypanosomes is seen and staining of thick and thin blood films, as for the detection of malaria, will reveal trypanosomes (Fig. 2). Where necessary concentration methods, with centrifuged citrated specimens of blood, should be used. In the earliest stages of gambiense infections the trypanosomes may be seen in the blood or from puncture of the primary lesion but it is usually easier to demonstrate them by puncture of a lymph node. Using a medium sized dry needle, the node, held between finger and thumb, is punctured and the node moved on the needle and the material aspirated and examined in a similar way to the blood. Animal inoculation and culture on a special medium can also be employed. A complement-fixation test with an antigen from *T. equiperdum* has been used to detect relapses of *T. gambiense* infections. Trypanosomes are only isionally found in the cerebrospinal fluid but examination of it is an ortant routine measure to assess, by the cell count and especially the protein tent, the degree of affection, if any, of the nervous system. Except in cases h undoubted established neurological abnormalities, lumbar puncture should deferred until the first dose of a trypanocidal drug has been given. This will uce the risk of implantation of trypanosomes into the cerebrospinal fluid, the lumbar puncture needle.

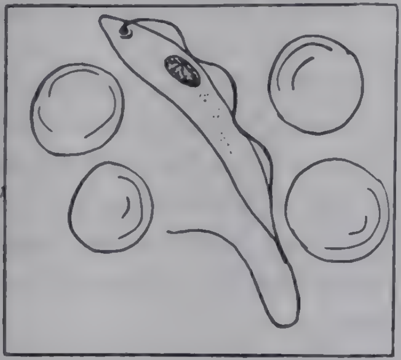


FIG. 2
Trypanosome in blood film.

Treatment. If treatment is begun early, before the brain has been invaded, will be curative. For this purpose either suramin or pentamidine isethionate ay be used, the latter being employed only for gambiense infections. After ie nervous system is affected an arsenical, e.g. melarsoprol, will be required as ıramin and pentamidine do not penetrate into the brain.

Suramin, a complex organic urea compound, is usually given intravenously. n initial trial dose of 200 mg is given to test for sensitivity. This is followed n the next day by 1 g dissolved in 10 ml of distilled water repeated at intervals f three to five days to a total dosage of 5 to 10 g. Children tolerate the drug vell, the adult dose of 1 g being reduced for a child under 3 years to 250 mg nd from 3 to 10 years to 500 mg given in a course similar to that recommended or adults. Toxic effects which may occur include dermatitis, nausea, vomiting nd peripheral neuritis. Also, as the kidneys may be affected the urine should e examined before each injection and the drug discontinued if red cells and asts appear.

Pentamidine isethionate, an aromatic diamidine, is less toxic than suramin. t is rather painful when administered intramuscularly but, as there may be udden collapse from a rapid fall in blood pressure when the drug is used ıtravenously, this route is not recommended. The intramuscular dose is 3 to mg/kg body weight to a maximum of 250 mg dissolved in 5 ml distilled water, n alternate days for 10 injections.

Melarsoprol is a chemical combination of the trivalent melarsan oxide and imercaprol. It is presented as a 3·6 per cent w/v solution in glycolpropylene nd is administered intravenously. Although a toxic drug, it has proved highly fficacious in advanced rhodesiense infections, which were formerly fatal, and or other resistant and relapsing cases. The main danger is encephalopathy ue to a Jarisch-Herxheimer reaction to the death of many trypanosomes. efore commencing treatment with melarsoprol the patient's general condition ıay be benefited by a few preliminary injections of suramin. The initial dose of melarsoprol is assessed on the patient's general condition rather than on weight. Patients who are severely ill may at first only tolerate as small a dose 0·5 ml of the 3·6 per cent w/v solution and the initial dose must never exce 2 ml. Further injections are given on the second and third days. The maximu dose is 3·6 mg/kg body weight, i.e. 5 ml of 3·6 per cent w/v solution for a m of 50 kg. There then follows a rest period of one to two weeks followed by second series of three injections. If the initial dose was very small, addition courses may be required during the next four or five weeks. The total dosa aimed at is 30 ml of the 3·6 per cent w/v solution. Melarsoprol should only given under medical supervision.

Melarsonyl potassium is a water-soluble derivative of melarsoprol suitab for intramuscular injection. It is less toxic than melarsoprol. The daily do is 4 mg/kg body weight administered as follows. As a test for sensitivity a ha dose is given, followed by three successive full daily doses. For intermedia and late cases, after an interval of 7 to 10 days a further four daily doses ar given. Good results have been obtained in gambiense trypanosomiasis. It is no a fully reliable drug for rhodesiense infections.

Nitrofurazone is liable to produce undesirable side-effects including haemolytic anaemia in those whose red cells are deficient in glucose-6-phosphat dehydrogenase but has occasionally been successful. It should only be use when all other drugs have failed. The adult dose is 500 mg orally three time daily for 10 days.

GENERAL MEASURES. Malnutrition and any concomitant infection should be combated.

Personal Prophylaxis. Against *T. gambiense* a single intramuscular injection of 250 mg pentamidine gives protection for six months because of the slow excretion of the drug. As the protection against *T. rhodesiense* is less sure and shorter in duration, chemoprophylaxis is not advised in rhodesiense areas as the infection may be masked until a late stage is reached. In such areas it is safer to have no protection but to ensure early recognition of the 'trypanosomal chancre' and to have the blood examined at monthly intervals or whenever there is any fever. Prompt treatment will then be curative.

AMERICAN TRYPANOSOMIASIS

(CHAGAS' DISEASE)

The cause of Chagas' disease is *Trypanosoma cruzi* transmitted to man from the faeces of a reduviid bug in which the trypanosomes have a cycle of development before becoming infective to man. They enter through the conjunctiva, mucosa of mouth or nose or through an abrasion of the skin. The bugs are liable to fly down from the ceilings of primitive houses on to the faces of those sleeping below. Dogs and cats are the most important hosts in nature although many wild and domestic animals may harbour the infection. Acute illness has also followed transfusion of infected blood.

athology. At the site of entry there is usually a local tissue reaction. The anosomes travel by the blood stream and develop into leishmanoid forms. se are liable to multiply in the myocardium causing pseudocysts in the cle fibres and also in the nervous system, giving rise to the changes described ow.

linical Features. The entrance of *T. cruzi* through an abrasion produces a ky-red firm swelling with enlargement of regional lymph nodes. Although common, a conjunctival lesion is more pathognomonic; the unilateral firm dish swelling of the lids may close the eye and constitutes 'Romana's sign'. dence of a generalised infection soon appears, young children being the st severely affected with the temperature rising to 40° C. and lasting for two eks or more. Tachycardia, always a feature, may persist for months. In dition to generalised lymphadenopathy there may also be enlargement of spleen and liver. Neurological features include insomnia, personality changes d signs of meningo-encephalitis. Chronic infections frequently damage ierbach's plexus with resulting dilatation of various parts of the alimentary nal, especially the colon and even including the appendix. Dilatation of the e ducts and bronchi are also recognised sequelae. Invasion of the myocardium uses a cardiomyopathy (p. **286**) as indicated by cardiac dilatation, dysythmias and partial or complete heart block. Only infants die readily from e acute infection, death being caused in the first few days of the illness by cephalitis or a few weeks later by myocarditis or an overwhelming generalised fection. In those who survive the acute phase the trypanosomes often persist, using a chronic illness from which a slow recovery takes place. Many cases e difficult to diagnose because there may be no apparent site of entry and ere may be no acute phase. Chagas' disease is being increasingly recognised, the endemic areas, as a cause of cardiomyopathy, responsible, on occasion, r sudden death particularly in adult males during exercise.

Diagnosis. A history of residence in an endemic area with suggestive symptoms dicates the need for a search for *T. cruzi* in the blood or for the leishmanoid rms in other tissues. The trypanosomes are often scanty in the blood but may e recovered by culture. Xenodiagnosis has been used with success. In this ethod infection-free, laboratory-bred, reduviid bugs are fed on the patient and vo weeks later and subsequently for periods up to one year the hind gut or eces of the bug are examined for metacyclic trypanosomes. A complement-xation test (Guerreiro-Machado reaction) has also been used as a means of agnosis. In acute cases a positive result can be expected but in chronic infections e results are less reliable.

Treatment. No fully effective specific remedy is available. Arsenobenzyl lphate is used in the hope of slowing down the progress of the infection. is given in a 10 per cent solution beginning with 150 mg for an adult, increasing adually to 450 mg up to a total of 5 g. An alternative which is used is tetracline, 2 g daily in divided doses, combined with primaquine 7·5 mg base ice daily, both for 14 days.

Prevention. Preventive measures should include improved housing a destruction of reduviid bugs by spraying of houses with lindane (gam BHC).

BALANTIDIASIS

Balantidium coli, a large ciliate protozoon, affects pigs and occasionally ma

Geographical Distribution. The infection is seen, but only infrequently, in countries among those who tend domestic pigs.

Pathology. The pathology is similar to that of intestinal amoebias *Balantidium coli* may live free in the lumen of the bowel or it may cau ulceration in the colon; in severe cases almost the whole extent of the low bowel may be affected and also the lower part of the ileum.

Clinical Features. The infection may be symptomless but when ulceratio occurs frequent stools are passed together with blood and mucus.

Diagnosis. *Balantidium coli* is recognised in the stool by microscopic examination.

Treatment. The disease usually responds to the arsenical Carbarsone, 250 mg given orally twice daily for 10 days. Other cases respond better to tetracycline 0·5 g four times daily for 10 days. In debilitated persons the disease may become chronic and the infection may be difficult to eradicate.

GIARDIASIS

(Flagellate Diarrhoea)

The human infection is due to *Giardia intestinalis*, a pear-shaped flagellate 12 to 18 microns in length (Fig. 3).

Geographical Distribution. It is world-wide in its distribution but more common in the tropics.

Pathology. The flagellates inhabit the small intestine and cause a mild enteritis.

Clinical Features. The infection is often symptomless but recurrent attacks of urgent diarrhoea with abdominal discomfort and loose pale stools are characteristic. In heavy infections there may be evidence of malabsorption.

Diagnosis. The symptoms might suggest sprue or intestinal amoebiasis but the flagellates, or during quiescent periods their cysts, are found on microscopic examination of the stool.

eatment. Metronidazole 200 mg or alternatively mepacrine 100 mg three s daily after food for seven days is given to an adult and the course may to be repeated after a free interval of one week. Children under four years ge can be given one-quarter of the adult dose and from four to eight years of the adult dose, of either drug.

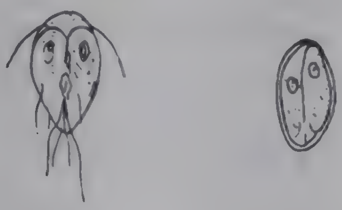


FIG. 3
Giardia intestinalis.
Vegetative and cystic forms.

TOXOPLASMOSIS

oxoplasmosis is caused by *Toxoplasma gondii*, a small protozoon. It is bable that human infection after birth results from the ingestion of cysts reted in the faeces of infected cats. Transmission from mother to foetus ses congenital toxoplasmosis.

eographical Distribution. Human toxoplasmosis occurs widely in North, ntral and South America, Europe, Asia and Africa.

Pathology. In the congenital form the organism is widespread in the central rvous system, eyes, heart, lungs and adrenals. If the infant survives, the rasite soon disappears from most organs except the central nervous system d eyes. The brain shows large areas of necrosis with cyst formation and tchy calcification; the spinal cord may be similarly affected. In adults the ions, confined largely to the lung, may produce areas of fibrosis.

Clinical Features. The manifestations in congenital infections are mainly ebral. There may be hydrocephalus or microcephaly associated with con- lsions, tremors or paralysis with resultant contractures. Radiological exam- tion may show patches of calcification in the brain. Eye defects, micro- thalmos, nystagmus and chorio-retinitis are common. The cerebrospinal fluid often xanthochromic with increased protein and mononuclear cells. An arged liver, jaundice, diminished thrombocytes and purpura may also be nd. Congenital infections are usually fatal, and if the child survives he is ally gravely incapacitated.

n acquired infections symptoms are more variable. Many are symptomless. the acute form there may be pneumonitis with fever, cough, generalised es and pains and inconstantly a maculopapular rash. In the more chronic ections, often afebrile, there may be only enlargement of the lymph nodes h a lymphocytosis showing atypical mononuclear cells similar to those sent in infectious mononucleosis. Toxoplasmosis is recognised as a cause of rio-retinitis and uveitis in adults.

Diagnosis. In congenital toxoplasmosis the neurological signs and symp suggest the diagnosis. The mothers from whom the infection is transm have symptomless infections. Serological tests are of value in indicatin presence of active or past infections. The dye test (Sabin and Feldman) bec positive early in the disease and persists for years. This test depends on finding that toxoplasma incubated with normal serum stain with methy blue, whereas if they are incubated with serum containing antibodies the not stain. The occurrence of positive tests in those free from symptoms ne sitates caution in their interpretation in relation to an individual clinical prob Biopsy material, such as that obtained from a lymph node, may yield *Toxoplasma* on culture or by inoculation of a laboratory animal.

Treatment. A combination of a sulphonamide 1 g six-hourly and p methamine 25 mg daily for two weeks has been shown to be beneficial in treatment of chorio-retinitis due to toxoplasmosis and should be administe in all active cases. If the infection is symptom-free, and there is no possibi of pregnancy ensuing, treatment is unnecessary.

seases due to Bacteria, irochaetes and Spirilla

GRANULOMA VENEREUM

(Ulcerating Granuloma of the Pudenda, Donovanosis)

nuloma venereum is a venereal disease due to *Klebsiella granulomatis*, acterised by intracellular Donovan bodies, 1 to 2 microns in size, demon- ble in the endothelial and mononuclear cells of the lesion.

he disease has a wide distribution throughout the tropics and sub-tropics.

athology. At the margin of the lesion there is infiltration of the superficial tion of the corium and of the papillae by lymphocytes and mononuclear s in which Donovan bodies can be demonstrated. Excessive fibrous tissue ormed especially in lesions of long standing.

linical Features. The incubation period is variable, from a few days to ee months after exposure. The primary lesion is a small nodule or papule the skin or mucous membrane of the external genitalia. This progresses to m a superficial serpiginous ulcer spreading peripherally. Auto-infection of opposing surface also extends the spread. Moist warm areas of the body, rticularly the flexures of the thighs, the folds between the scrotum and thighs the male and the labia and vagina in the female, are especially vulnerable. e perianal region and occasionally the face and mucous membrane of the outh, in addition to the genital area, may also be affected. Untreated, the sions may continue for years, spreading at the periphery and leaving an healthy scarred area which tends to break down from slight trauma.

Healing of the ulcer is often associated with excessive fibrous tissue formation hich may lead to scarring and stenosis of the urethra, anal orifice or vagina. e lymph nodes, however, are not affected, and constitutional symptoms are ght or absent. A few cases of generalised donovanosis have been reported.

Diagnosis. A chronic superficial spreading ulcer in the genital region without y enlargement of the lymph nodes should suggest the disease; the detection Donovan bodies is diagnostic.

Treatment. Streptomycin 1 g daily for 7 to 14 days intramuscularly or tetra- cline for 10 days orally is the treatment of choice. Surgery may be needed alleviate the effects of scarring.

BARTONELLOSIS

(Carrión's Disease, Oroya Fever, Verruga Peruana)

This disease is caused by a small organism, *Bartonella bacilliformis*, trans- tted by sandflies.

Geographical Distribution. It is prevalent in narrow hot valleys on the wes slopes of the Andes at heights between 2,000 and 10,000 feet. Thus it is fo in Peru, Ecuador, Bolivia, Colombia and Chile. The distribution coinc with the presence of the sandflies, *Phlebotomus verrucarum* and *P. noguchi*, it is possible that the disease may also be transmitted by lice and ticks.

Pathology. In the acute form of the disease, Oroya fever, there is sev haemolysis. The spleen, liver and lymph nodes are enlarged. The bone marr shows normoblastic hyperplasia, but megaloblastic changes have also b described presumably due to folic acid deficiency. Bartonellae are present large numbers, often in clumps, in the erythrocytes and also in the endothe cells lining the small vessels of the spleen, lymph nodes, adrenals, kidne bone marrow and elsewhere. There are necrotic foci in the liver and sple In the later stage of the disease, verruga peruana, cutaneous nodules for microscopically resembling haemangiomas but containing scanty bartonel in the endothelial cells.

Clinical Features. After an incubation period of 14 to 21 days the ear stage, Oroya fever, develops with a sudden rise of temperature to 40° C ar rapid haemolysis leading to progressive pallor and prostration. The fever accompanied by pains in muscles and joints, nausea, vomiting and diarrho and may terminate in delirium and coma. The red cell count may fall to o million in four days. Bartonellae are seen in stained blood films and in seve infections over 90 per cent of the erythrocytes contain from 1 to 50 or mo organisms. The anaemia is macro-normoblastic, with anisocytosis, poikil cytosis and polychromatophilia and many reticulocytes, normoblasts and pronounced neutrophil leucocytosis. The spleen and liver are enlarged an tender. Secondary infection by salmonellae is a frequent cause of death. Th first stage lasts from one to three weeks. In those who survive, the bartonella soon disappear and the destroyed red cells are rapidly replaced. Cultures o the blood taken over a period of months may, however, continue to yield the organisms. Untreated the mortality in the acute form of the disease, especiall prevalent in children, is over 90 per cent.

The cutaneous form, verruga peruana, usually follows 30 to 40 days after the febrile phase but occasionally there is no preceding fever. The eruption consists of cherry-red haemangioma-like cutaneous nodules 2 to 10 mm in diameter. They are distributed peripherally on the head and limbs. Occasionally there may be a number on the mucous membrane of the mouth and pharynx. The cutaneous lesions are oval or rounded and lie half-buried in the skin. They are covered with a bluish epidermis which may ulcerate after slight injury. These lesions often appear in crops but they heal completely in two to three months. This stage is never fatal.

Diagnosis. The diagnosis is suggested by the clinical picture in an endemic area and is confirmed by the demonstration of bartonellae in the erythrocytes. In the verruga stage the organisms are found in the endothelial cells in biopsy tissue. Blood cultures may be positive in both stages.

eatment. In the early febrile stage penicillin, streptomycin or tetracycline ve days give good results. Blood transfusions, fluids and electrolytes may rgently required. If the anaemia is megaloblastic hydroxocobalamin or acid should be given (p. **727**). The cutaneous lesions require no local ment except, occasionally, haemostasis.

ersonal Protection. The use of insecticides, insect repellants and suitable ective clothing is advisable (p. 46).

MELIOIDOSIS

lelioidosis is caused by *Pseudomonas pseudomallei*, a micro-organism closely ted to *Ps. mallei*, the cause of glanders, which is a rare disease of horses grooms. *Ps. pseudomallei* is found in puddles following recent rain which gests it may be saprophytic in nature. Observations suggest that many ctions are acquired through abrasions of the skin although the respiratory alimentary routes may also be possible. Diabetics and patients with severe ns are particularly vulnerable to infection.

Geographical Distribution. The disease has been increasingly reported from Far East and Malaysia but also from Africa, Australia and elsewhere.

Pathology. A bacteraemia results in the formation of abscesses in the lungs, er and spleen. In more chronic forms multiple abscesses continue to recur in bcutaneous tissue in addition to internal organs.

Clinical Features. In the majority there are high fever, prostration and signs pneumonitis, with enlargement of the liver and spleen and sometimes ysenteric symptoms. A radiograph of the lungs resembles that of acute seous tuberculosis. In the chronic forms multiple abscesses develop.

Diagnosis. The disease may be suspected from the clinical and radiographic ppearances, and in acute cases blood culture or culture of the sputum may ield *Ps. pseudomallei* which can also be recovered from abscesses in the more hronic disease. Except in fulminating infections antibodies, which are common lso to those produced in glanders, may be detected by agglutination and omplement-fixation tests. A haemagglutination test is more sensitive and is pecific for *Ps. pseudomallei*.

Treatment. Prompt treatment, without waiting for cultural confirmation, ith tetracycline 3 g daily or carbenicillin in large doses daily, has cured some arly cases and these antibiotics or a sulphonamide as indicated by sensitivity ests assist recovery from more chronic infections. In addition, if subcutaneous r deep abscesses have developed their drainage is required.

LEPROSY

Leprosy is a chronic granulomatous disease caused by *Mycobacterium leprae*, n acid- and alcohol-fast organism that resembles *Myco. tuberculosis* in many ways. Widespread lesions of lepromatous leprosy have been reproduce irradiated and thymectomised mice. Local multiplication of the organis the foot-pads of mice is proving a most useful technique for demonstra the identity and viability of *Myco. leprae* and the existence of drug-resis strains, the screening of drugs, the effect of BCG vaccination, and for study of cell-mediated immunity. The mode of entry of *Myco. leprae* into body has not been conclusively proved; it is generally assumed that the orga may pass through damaged skin or respiratory mucosa. Most patients gi history of prolonged association, especially in childhood or adolescence, someone suffering from an open form of leprosy. The silent (or incubat period is usually between two and five years.

Geographical Distribution. The disease is common in tropical Asia, the East, tropical Africa, Central and South America, and in some Pacific Isla and the total number of people affected with leprosy is estimated at 15 milli

Pathology. The organisms show a predilection for nerve tissue, skin and mucosa of the upper respiratory tract. The reaction of the host to their prese varies within the widest limits. In *tuberculoid leprosy* there is a marked cellu response, indicative of a vigorous defence, around nerves, sweat glands and h follicles. Organisms are scanty, and found mainly in the vicinity of termi nerve endings in the dermis. They are seen only after prolonged search or the use of concentration techniques. Lymphocytes, histiocytes and epithel cells, some coalescing to form giant cells, are grouped in foci resembling tubercl but without central caseation. In contrast to the typical picture in lepromato leprosy, the cellular infiltration may extend to and through the subepiderm zone. Tuberculoid leprosy is usually considered to be non-infective.

In *lepromatous leprosy*, the infective form of the disease, organisms a present in great abundance in the dermis, eventually replacing the norm architecture. They are mainly grouped in 'globi', which are large macrophage containing 50 or more organisms, and are found in nerve tissue, the arrectore pilorum muscles and the endothelial cells of blood vessels; rarely in the cell of the epidermis itself. They are carried in the blood stream (in which they ca be demonstrated) to distant and deep organs including muscles, lymph nodes bone marrow, Kupffer cells of the liver and the spleen. Terminal amyloid disease is not uncommon.

Between these two 'polar' types of leprosy, there are diverse intermediate manifestations grouped under the terms '*borderline*' or '*dimorphous*'. The host reaction varies within wide limits from the near-lepromatous to the near-tuberculoid; it may vary also from time to time in the same patient. The early infection, usually transient, and either self-healing or giving place to one or other of the determinate types, is called '*indeterminate*'. The histological appearances in it are non-specific, and consist of groups of round cells diffusely scattered in the dermis. *Myco. leprae* are demonstrable in varying numbers in borderline and indeterminate leprosy. The differing tissue response is usually paralleled by the reaction in the lepromin test which determines sensitivity to an intradermal injection of a sterilised extract of lepromatous tissue. Positive ions are obtained in tuberculoid leprosy, a negative response in lepro- us leprosy and negative or weak positive responses in indeterminate and erline leprosy. This test is of no value in establishing the diagnosis of sy since positive results are also found in those who have had BCG ination and in many normal people, but it is useful in helping to classify lifferent tissue responses in leprosy.

he most serious results of leprosy infection consist in peripheral neuropathy, its sequelae. The principal mixed nerve trunks of the limbs and face may everely damaged in their superficial course. The damage is due to cellular tion to degenerating leprosy bacilli, rather than to the presence of living nisms, and is shown clinically by distal sensory and motor deficits, with ltant mutilations, contractures and muscular atrophy.

ny determinate form of leprosy may undergo an exacerbation, loosely ed a 'reaction', which is regarded as caused by obscure variations in the ence mechanism.

linical Features. The disease usually becomes manifest insidiously, although asionally it does so more abruptly. The most common first symptom is a all but persistent area of impaired sensation. In other cases the first noticeable ture may be macules, which are usually hypopigmented and erythematous. *uberculoid leprosy* is arbitrarily classified into three types, macular, minor d major tuberculoid. The tuberculoid macule has clear-cut definite margins; surface is smooth and dry and exhibits some loss of sensation, tactile and rmal appreciation being early impaired. Sensory impairment may not be ident in lesions of the face. The macules are often multiple but asymmetrical. mmon sites are the lateral aspects of the arms and legs, the buttocks and oulders. Minor tuberculoid lesions are slightly raised, particularly at the argin. By extension, large areas may be affected. The distribution is similar that of macular tuberculoid lesions. Some of the superficial cutaneous rves supplying the affected areas may be enlarged and tender. Major tuber- uloid lesions are larger than minor lesions, and more raised; the centre may atrophic and flattened, while the edges are raised and advancing. These sions exhibit loss of appreciation to all three superficial sensory stimuli, loss sweating and, on exposure to cold, lack of contraction of the arrectores lorum muscles. Related nerve trunks are typically enlarged, hard and tender sites of predilection.

The main complications of tuberculoid leprosy are the result of accompanying ripheral neuropathy resulting from cellular infiltration, leading to fibrosis d sometimes caseation in the nerves. A combination of fifth and seventh anial nerve damage produces an exposed anaesthetic eye very liable to loss sight from trauma and infection. In the upper limbs destruction of the ulnar rve may lead to a claw hand and ulceration of the phalanges. Evidence of largement of the great auricular, ulnar, lateral popliteal or other nerves, is a luable aid in diagnosis. Osteomyelitis consequent upon infection through abrasion in an insensitive area may cause the loss of terminal portions of gits, but more commonly the phalanges are absorbed until the finger nails ay appear to arise from the knuckles. In the lower limbs foot-drop and aumatic lesions of insensitive feet are very common.

The macule of *indeterminate leprosy* is an inconspicuous lesion 2 to 3 diameter, situated anywhere on the body, exhibiting slight pigmentary sensory changes. This lesion often heals spontaneously.

Borderline or *dimorphous leprosy* may present as annular lesions of bi shape with ill-defined outer margins, or by plaques and succulent lesions raised at the centre than at the periphery.

Lepromatous lesions of the skin are described as they progress from to late lesions, as being macular, infiltrative, diffuse or nodular. Leproma macules are numerous, hypopigmented, erythematous, and very slig infiltrated. They differ from tuberculoid macules in that they are small, wi scattered on the body, usually symmetrically, and the margins of the mac merge imperceptibly with normal skin. Sensation in them is not impai They are often inconspicuous except to the trained eye and to local inhabit who are often familiar with the signs that herald grave leprosy. Altho clinically the lesions are not very obvious, the diagnosis is not difficult *Myco. leprae* are numerous in the skin and can be demonstrated by skin as described below. As the disease advances, the macular lesions becc infiltrated and succulent in appearance; in advanced lepromatous lepr nodular lesions appear, especially on the ears and face. A less common ma festation of lepromatous leprosy is diffuse symmetrical thickening of the sk often with thickened lobes of the ear, producing 'leonine facies'.

With advanced lepromatous disease 'glove and stocking' peripheral ana thesia is frequently present, but nerve damage occurs typically later than in other determinate forms of leprosy. The outer third of the eyebrows is oft lost. Impairment of sweating occurs.

The following extradermal lepromatous lesions should be noted. The tes may be destroyed and gynaecomastia ensue. The mucous membranes of t nose, mouth and trachea may ulcerate, and late deformities may result fro necrosis of the cartilage and bones of the nose and oral cavity and loss of tl upper incisor teeth. The lips and face may be grossly misshapen. Adjace lesions may spread into the eye but, more commonly, this is infected throug the blood stream. The most frequent lesions in the eye are miliary lepromat on the iris and accompanying superficial punctate keratitis, but any part of th eye may be affected although the retina only very rarely. An acute irido-cyclit frequently supervenes during the acute exacerbation of lepromatous leprosy.

Reactions. Untreated leprosy does not show a steady progression. Man patients with tuberculoid leprosy overcome the infection with minimal residua signs. Lepromatous leprosy tends to smoulder for a time with gradual pro gression but, after the disease has become extensive, 'lepra reactions' ma ensue. These are characterised by fever, exacerbation of existing lesions and th appearance of new ones and of an eruption aptly called 'erythema nodosun leprosum'. In addition, subcutaneous nodules, iritis, orchitis, lymphadenitis. ulceration of nodules, pain in nerves and oedema of extremities may develop. During the lepra reaction the ESR rises. After the reaction has subsided the disease will be found to have extended. A series of such reactions may lead the patient gradually towards death. In tuberculoid leprosy, too, reactions may occur and these are very liable to be precipitated by large initial doses psone, or over-rapid increments. The reactions consist of exacerbation sting skin lesions with surrounding oedema and an increase of organisms ring the patient temporarily infective. Lesions become hypersensitive, swollen peripheral nerves, constricted at places by the epineurium, may tremely painful. In summary, pain rather than fever or toxicity is prenant. Reactional states are attributable to inadequate or disordered defence anisms. In tuberculoid leprosy it may be an 'up-grading' reaction leading gression of the disease, but during the reactions damage of importance be sustained, especially in nerves or the eye, and unstable intermediate s may exhibit a loss of immunity progressing towards the lepromatous Some reactions, however, are mild, consisting chiefly in swellings of hema nodosum leprosum', each lasting for only a few days but recurring several months.

agnosis. There are many causes for the appearance of macules but a pigmented macule with a well-defined edge associated with sensory ges, which cannot be attributed to scarring, is very suggestive of tuberid leprosy. If such a lesion is associated with definite enlargement of nerves nical diagnosis needs no further confirmation. *Myco. leprae* are unlikely e demonstrable in the skin but a biopsy taken from the edge of a lesion show the characteristic histology. A nerve biopsy will demonstrate cellular tration and sometimes the organisms, but this is seldom necessary for nosis.

epromatous leprosy is readily diagnosed by the demonstration of *Myco. ae* stained by a modified Ziehl-Neelsen's method in material obtained from deeper layers of the skin on the point of a scalpel introduced through a small in the skin. A smear made from a fragment of mucosa obtained from the al septum may contain characteristic globi of *Myco. leprae*. The presence *Myco. leprae* distinguishes lepromatous leprosy from other diseases of the n, e.g. diffuse cutaneous leishmaniasis (p. 5).

here are very few conditions other than leprosy that gives rise to enlargent of nerves. Local enlargement may be due to a neuroma or trauma. Wasting y make nerves more easily palpable than normally; hence, asymmetrical argement is of particular clinical significance. Enlargement of one or more ves may occur in primary amyloidosis. Familial hypertrophic neuritis is a e familial disorder. An over-anxious wearer of a bush-shirt who rests his ows on a desk may need reassurance that his palpable ulnar nerves are not hologically thickened. Usually the polyneuritis of leprosy is associated with aneous lesions but in some countries pure 'neural forms' are not uncommon. ingomyelia may be simulated, but the sensation of touch is lost early in rosy and retained in syringomyelia, which may also be associated with er motor neurone lesions in the lower limbs.

reatment. To enable specific treatment to be carried out successfully it is ortant to win the confidence and collaboration of the patient. Multiplication *Myco. leprae* is inhibited by dapsone (diamino-diphenylsulphone, DDS) en orally. Clinical observations and recent experimental work indicate that

only very small doses are required, although the emergence of organisms sh
resistance to dapsone indicates that there may be a danger in using mini
effective doses. Toxic effects of the drug and precipitation of reactional
are much less likely to occur, however, if small doses are employed. I
usually be appropriate to administer 25 mg weekly, increasing this by 2
weekly, until a dose of 50 mg twice weekly is reached. For lepromatous le
double this dose may be required, i.e. 100 mg twice weekly or 25 mg
For children under 5 years, one-fifth of the adult dose, and from 5 to 12
one-half of the adult dose should be prescribed.

In tuberculoid leprosy the tendency is towards arrest, but cure ma
hastened and deformity prevented by early treatment with dapsone.
should be continued for a minimum of 2 years and for not less than 12 mo
after apparent cure. Patients with borderline leprosy require careful su
vision and cautious treatment. The clinical manifestations of lepromat
leprosy may be dramatically affected or response may be extremely slow,
in any case treatment must be continued for at least 2 years after skin sm
are negative. The patient must be prepared to accept treatment lasting
many years and perhaps for life. Follow-up is essential as relapses h
been reported, especially in patients with borderline leprosy, inadequa
treated.

The proportion of the normal to the degenerate bacilli is called the morp
logical index, which is one indication of the bacteriostatic activity of the d
used, and hence a criterion for eventual clinical improvement. Morphologic
normal bacilli ('solid rods') usually disappear in a few months from the s
from which smears are taken, and such patients may thereafter be conside
to be non-contagious.

Toxic effects, which are largely avoided by the above cautious regime, incl
anaemia, dermatitis, erythema nodosum leprosum, neuritis, hepatitis a
psychosis. Pain due to swelling of the nerve may be distressing and may
followed by increased neural damage (see below).

Thiambutosine is a satisfactory substitute for dapsone. The dose is 500
(1 tablet) daily for a fortnight increasing by 500 mg fortnightly to a maxim
of 2 to 3 g daily. It is less liable to cause toxic effects than dapsone but dr
resistance may occur after two years of treatment with it.

Some long-acting sulphonamides (e.g. sulfoxine) are widely used in so
countries.

Patients who do not tolerate dapsone may be treated with considera
success by a combination of isoniazid and streptomycin which is also indicat
if there is a concomitant tuberculosis. Rifampicin, of proved value in th
treatment of tuberculosis, has recently been used successfully in lepros
Clofazimine is particularly indicated in the treatment of reactional states (s
below).

Those with areas of anaesthesia (thermal and tactile) must be given caref
instructions regarding measures to prevent damage to the affected part. Physic
therapy should be started early in the disease. Orthopaedic measures are ofte
necessary to correct deformities resulting from damaged peripheral nerve
Thus ideally every patient with neural damage should be early subject t
orthopaedic control.

ATMENT OF REACTIONS IN LEPROSY. If the patient is suffering from hepatitis, chosis or an allergic dermatosis attributable to dapsone, this drug should topped. In other cases of active leprosy in which the dose of dapsone ot been too high, it or an alternative antileprosy drug should be continued. ofazimine is valuable in that it exerts an anti-inflammatory effect and is e same time bacteriostatic. It does, however, produce a ruddy complexion tends to cause dark pigmentation in areas of skin already affected by sy. This may make the drug unacceptable to some, but the relief obtained outweigh the disadvantages. A dose of 100 mg three times daily will lly suffice to control a reaction. When clofazimine is used, it is seldom ssary to incise the epineurium of swollen nerves or to inject hydrocortisone the sheath.

r patients in whom clofazimine cannot be given, older methods should ttempted. Chloroquine 150 mg (base) three times daily for two weeks or, ere is no response, a trivalent antimonial, such as Stibophen, 2 ml intra-cularly on alternate days for six doses should be tried.

severe reactions, if clofazimine is declined or fails, corticosteroids, e.g. nisolone 25 mg daily, will usually give relief, but there is great difficulty ithdrawing the corticosteroid without risking a rebound exacerbation. If one has been stopped, thiambutosine may be substituted temporarily.

idocyclitis, associated with erythema nodosum leprosum, must be treated dilating the pupils with 1 per cent atropine drops morning and evening, le hydrocortisone eye drops (1 per cent solution) are applied hourly until inflammation subsides. If the patient is not having systemic corticosteroids 8 mg of hydrocortisone dissolved in 0·3 ml sterile normal saline may be cted subconjunctivally. When there is an open corneal ulcer corticosteroids uld be given cautiously and then only with an antibiotic.

ENERAL MANAGEMENT. In Britain the disease is notifiable. Voluntary segre-ion is rarely indicated for lepromatous patients before treatment is established hough initiation of treatment in an institution is often beneficial. Good d, regular exercise and efficient treatment of intercurrent diseases such as erculosis, dysentery, malaria, kala azar and helminthic infections are portant. The morale of patients should be maintained by providing social enities, schools, vocational training and, where possible, agreeable and unerative occupation.

ersonal Prophylaxis. Children should not come into close or repeated tact with open leprosy. Medical staff should take the ordinary precautions washing of hands with soap and water and wear rubber gloves and gowns en engaged in activities necessitating prolonged contact with the skins of ients with lepromatous leprosy. Dapsone prophylaxis is generally neither essary nor desirable but a child who has been in close contact with a lepro-tous parent may be given oral dapsone for two years after exposure has sed. Since there is some evidence that BCG vaccination may protect ut three-quarters of children exposed intrafamilialy to leprosy, BCG cination should be offered to child contacts of patients with lepromatous rosy. However, the reduction of the reservoir of infection by mass treatment,

concentrating on patients with lepromatous and borderline leprosy, ap
to offer at present the best prospect of control of the disease in the comm

CHOLERA

Cholera, an acute disease of the gastrointestinal tract, is caused b
contamination of food or drink by strains of *Vibrio cholerae*. There are diff
serotypes named Inaba, Ogawa, Hikojima and also the biotype eltor (ser
Ogawa), which since 1961 has become widespread throughout the Far
Near East and appears to be displacing the classical *V. cholerae* from
areas and in 1970 spread to Africa. Sporadic infections imported by trav
have appeared in European countries, including Britain, and infection
eating shell-fish has been proved. Formerly thought to be of low pathogeni
its virulence is now found to be equal to that of other strains. These dis
producing vibrios have to be distinguished from the many non-pathog
cholera-like vibrios. The most important endemic foci of cholera are in
lower reaches of the Ganges and Brahmaputra rivers. In these areas epide
of cholera are likely during the hot moist season when large numbers of pec
such as pilgrims, congregate and live in overcrowded and unhygienic conditi
and the disease may spread widely when people incubating it return to t
scattered homes. *Vibrio cholerae* usually disappear from the stools of pati
within a week of convalescence but exceptionally they may persist up t
month after the acute attack and *V. eltor* may exceptionally continue to
excreted for years. The disease appears to be maintained in endemic areas
very mild infections in a population with a considerable resistance to it.

Pathology. Apart from the shrinkage of organs and tissues through inte
dehydration there is acute diffuse enteritis principally in the small bowel. T
capillaries in the intestinal villi are widely dilated; the mucosa, pinkish a
coated with mucus, is infiltrated by lymphocytes and the submucosa is oft
odematous. The great loss of fluid and electrolytes from the bowel and mass
outpouring of hepatic and pancreatic secretions cause intense dehydratic
haemoconcentration and acute renal failure. Cholera vibrios do not inva
the blood stream but are found only within the superficial layers of the intestin
wall and in its dejecta. Investigations indicate that the local changes in t
mucosa of the small intestine are caused by cholera exotoxins and that t
vibrio endotoxins on absorption aggravate the hypotensive state brought abo
by loss of body fluids.

Clinical Features. After an incubation period of a few hours to five da
severe diarrhoea without pain or colic, followed by vomiting, usually begi
suddenly. This is characteristically effortless, fluid gushing from the bowel a
from the stomach. After the faecal contents of the gut have been evacuat
the typical 'rice-water' material is passed. This consists of flakes of mucus floati
in water. In severely ill patients, which includes most cases of cholera,
enormous quantity of fluid and electrolytes is rapidly lost. This soon leads
intense dehydration with agonising muscular cramps. Soon the patient pas
into the 'algid stage' with a low surface temperature, although the rec

rature may be up to 39° C. Cardiovascular collapse and prostration
accompany a very low blood pressure and a pulse which is barely per-
ble; the urine output is very scanty or absent. The body surface is cold
lammy, the eyes sunken and the skin wrinkled. The patient, however,
ly remains mentally clear. Unless fluid and electrolytes are replaced early
n adequate amounts the patient may die from acute circulatory failure
n 24 hours of the onset of the disease. With proper treatment, however,
vement can be expected, the diarrhoea and vomiting cease, the pulse
lood pressure improve, urine output increases and the 'stage of reaction'
n. During this stage the patient may develop hyperpyrexia or, if the fluid
ot been replaced in time, complete suppression of urine may lead to death
uraemia.

though this is the typical picture of cholera, other rare types of the disease
be encountered varying from a mild illness with only slight diarrhoea—
ulant cholera'—to a very intense illness—'cholera sicca'—in which the
nt is overwhelmed by the infection and the rapid loss of fluid into the
ed bowel and dies before typical gastrointestinal symptoms appear.

children under 12 years of age the mortality rate is higher (15 to 17 per
) than that of adults (4 to 6 per cent). Pulmonary oedema, febrile reactions
herapy, pyrexial convulsions and encephalopathy, tetany, meteorism, hypo-
aemia, hypernatraemia, acidosis and water retention and frequently mal-
ition are believed to be the adverse factors in paediatric practice. Over-
ration and respiratory complications, more common than in adults, may
play a part. Consideration of such factors and of the delicate physiological
biochemical balance in children have led to modifications in their manage-
it and treatment (p. 26). These methods have lowered the mortality to slightly
w the adult level of 4 per cent.

iagnosis. During a cholera epidemic the diagnosis is usually easy. It is,
vever, important that an atypical case should be recognised early so that
outbreak may be brought rapidly under control. Microscopic examination
the stool will detect the typical cholera vibrio, and culture of the stool or
ectal swab on special media is used to isolate the organism and determine
serological characteristics. Other diseases such as acute bacillary dysentery,
al enteritis, *P. falciparum* malaria, food poisoning and certain chemical
sons may produce symptoms like those of cholera. Cholera is notifiable
ler the International Health Regulations.

reatment. Three days treatment with tetracycline 250 mg six-hourly or
azolidine in single daily doses of 400 mg is of limited value in expediting
disappearance of the vibrios from the stools. The chief aim in treatment,
vever, is to maintain the circulation and prevent acute renal failure. This
be achieved by replacement of the great loss of water and electrolytes;
earlier this is started, the better is the prognosis. A clinical assessment of
patient's need in terms of water and electrolytes can be made from the
earance of the patient, the pulse, blood pressure, the output of urine and
n information regarding the volume of fluid lost by diarrhoea and vomiting.

Severe depletion of water and salt is usually rapid and this causes dang dehydration.

In adults replacement should be provided by intravenous isotonic s and in severe dehydration a total of 20 litres or more may be required to good the loss. In such cases as much as 2 litres, by the intravenous route, be given in the first hour and 1 litre in the second and in the third hour the veins are contracted it is usually necessary to introduce a cannu preferably a polythene tube into a large vein. Subsequent fluid is give indicated by the condition of the patient, a careful watch being kept for of pulmonary oedema and on the urinary output. To counteract acido is necessary during hydration to give 1 litre of isotonic (18·7 g per litre) so lactate solution for every 2 litres of isotonic saline. If modern facilities for the correct sterilisation and storage of isotonic sodium bicarbonate solu (14 g per litre), this solution is now considered preferable to sodium la solution as, with the latter, lactic acid acidosis may develop in conditio shock. Should hyperpyrexia occur, corticosteroids may help to control it, they may also be of value for a severely shocked patient.

The rectal temperature, and fluid loss in vomit and stool, and outpu urine should be carefully recorded. Stools should be collected in a calibr plastic receptacle under a 'cholera cot' which has a central reinforced and funnel, over which the patient's buttocks are placed. When there is do about the need for further fluid, an estimation is made of the patient's wh blood specific gravity using the copper sulphate drop method. A rise in spec gravity of 0·001 above the normal 1·055 indicates a lack of approxima 150 ml of fluid in a man weighing about 70 kg. Once vomiting has cea as much fluid as possible should be taken by mouth. Fluids given by an in gastric drip may successfully reduce the quantity of intravenous fluid requir

It is safer not to replace potassium loss until the kidneys have started function freely. Then potassium citrate 2 to 4 g should be given three ti a day by mouth or 10 mEq (0·75 g) potassium chloride can be added to e litre of the intravenous fluid. In Pakistan good results were obtained by intravenous infusion of an aqueous solution containing in each litre sodi chloride 5 g, sodium bicarbonate 4 g, potassium chloride 1 g. The 'milk' green coconuts is a useful source of potassium for oral administration. Anu makes the prognosis very grave. Treatment should be given for it as reco mended on page **610**. Favourable results from the use of corticosteroids ha been reported in a limited number of cases of cholera.

In children quick initial hydration is required but after the critical sta has passed overhydration, failure of correction of acidosis or a sudden swi to alkalosis may produce a fatal result. Therefore, although the principl remain the same as in adult therapy, certain modifications are require Calculation of fluid requirements on the basis of the specific gravity of who blood or plasma are excessive for a child of body weight less than 15 k Limb veins are extremely difficult to find in the collapsed child, therefore scalp vein or the external jugular vein should be selected for infusion. Intr peritoneal infusion has been found effective in the very young, but cholera relatively uncommon below the age of 6 months. Ringer lactate (BP) wi pH adjusted to 7 is the fluid of choice and is given at a rate of 30 ml/kg bo t in the first hour, but this may be varied according to the severity of ration and is thereafter regulated to replace the fluid loss in vomit, stool rine. Glucose water by mouth is given as soon as tolerated. Tetany, conns and hypoglycaemia may also require treatment.

e convalescence sets in it is rapid and uneventful.

sonal Prophylaxis. All discharges and soiled articles of clothing must be ected. Gloves should be worn by nursing attendants. Drinking water d be boiled, all food cooked and both protected from flies. Vaccination a killed suspension of *V. cholerae* should be given in two doses, 0·5 and l with an interval of one to four weeks. It is an international requirement avellers passing through endemic zones to be in possession of a certificate ccination which becomes valid six days after the first dose and lasts for onths. A single dose of vaccine may not produce a high degree of individual unity, but combined with an awareness in the community for the need mproved hygiene mass vaccination may lead to the abrupt cessation of utbreak.

me cholera vaccines produce cross-agglutination with brucellae, and this subsequently confuse investigations of a fever.

ANTHRAX

or centuries anthrax has been known as a disease of domestic animals. y become infected by inhaling or ingesting spores. The *Bacillus anthracis* ed in faeces forms spores in the presence of oxygen which become widely eminated by air currents. Grazing lands remain infective for years and necessary to bury infected carcasses deeply to avoid contamination of the

n man it is an occupational disease of farmers, butchers and dealers in es, animal hair and wool and handlers of bone meal from endemic areas. primitive conditions, where skins are used as sleeping mats, for clothing or carrying water, and where diseased cattle are eaten, the infection occurs emically.

he primary lesion in man may be in the skin, pharynx, larynx, lung or stinal tract, from any of which sites the infection may spread to lymph es and lead to a bacteraemia with demonstrable changes in the spleen, s, meninges and brain. The microscopical changes are those of haemorgic inflammation with areas of necrosis and interstitial oedema. There is a rophil leucocytosis of the blood and infiltration in the tissues without ess formation.

animals the disease may run a fulminating course, causing death from yxia in a few hours to several days, or be more prolonged with the formation carbuncle or a swelling around the neck or shoulders.

man there is an incubation period ranging from one to three days, or commonly, up to 10 days. When the infection is acquired from a skin or or from handling or slaughtering an animal, a cutaneous lesion indicates ortal of entry. This usually takes the form of a solitary 'malignant pustule' on an exposed part of the body, commonly the face. It begins as an i papule which enlarges and forms a vesicle filled with serosanguineous surrounded by gross oedema. The lesion is relatively painless and accomp by enlargement of regional lymph nodes. The vesicle dries up to form a black 'eschar' surrounded by blebs. In endemic areas patients may e only slight constitutional symptoms but in non-immune persons the lesi accompanied by high fever and toxaemia and if the sufferer is not energet treated an overwhelming bacteraemia may prove fatal within a week overcome only after a stormy and more prolonged illness. Occasionally may be no localised pustule but only oedema.

When infected meat is eaten, an ulcer with much surrounding oedema be seen in the pharynx or more commonly the infection causes a severe ga enteritis which frequently terminates fatally. Some people, usually of an age, escape unscathed after eating infected meat, presumably becaus previously acquired immunity.

Those who acquire the infection by inhalation, 'wool-sorters' disease', develop an acute laryngitis or a virulent haemorrhagic bronchopneum The disease may also present as meningitis.

Diagnosis. The appearance of a cutaneous lesion and the environmental occupational history should suggest the diagnosis. A stained smear of f taken from the edge of a malignant pustule demonstrates the organism, w may be confirmed in an atypical case by culture and pathogenicity tests mice, rabbits or guinea-pigs. *B. anthracis* is also recoverable from laryn and pulmonary anthrax and from the CSF in meningitis. If a group of pe who have feasted on an animal which has sickened and died are taken abru ill with fulminating gastroenteritis, anthrax should be suspected.

Post-mortem examination is not to be lightly undertaken because of risk of spreading the infection, but the mere demonstration in the faeces an organism resembling *B. anthracis* requires cultural confirmation as the n pathogenic *B. subtilis* is a common inhabitant and is morphologically simil Suspected animal products can be investigated by the addition of anthr immune serum to a clear extract of boiled tissues, a precipitate forming wit 15 minutes if the tissue is infected.

Treatment. *B. anthracis* is sensitive to most antibiotics. Effective treatme consists in giving penicillin or tetracycline in combination with streptomyci in full doses, for three to five days. In the presence of urgent symptoms, if anti-anthrax serum of known potency is available it should be administer intravenously, in a dose not exceeding 50 ml.

Prevention. The disease is controlled in cattle by slaughter and deep buri of the diseased animal, by the administration of prophylactic antiserum healthy animals at risk and by annual immunisation with attenuated culture Imports from endemic areas should be subject to strict control and sterilisation A vaccine is used to protect laboratory workers.

PLAGUE

ue is caused by *Yersinia pestis* and is primarily an infection of rodents. ganisms are transmitted between rodents by fleas (*Xenopsylla* spp.) and e death of a rat an infected flea may leave it and bite man. While feeding, regurgitates the organisms from its proventriculus, blocked by plague and thus infects man. In some countries wild rodents are the main nd from time to time the infection spreads from them to domestic rats ence to man. There is serological evidence that the infection may be ed by other animals, e.g. dogs, during outbreaks. In man the bacteraemia ause pneumonitis with the expectoration of *Y. pestis*. Thus the infection e spread from man to man by aerosols, the condition then being called monic plague'. This condition can also be caused by the accidental tion of a laboratory culture or dust containing viable organisms from d rodents.

hology. Rarely a vesicle with surrounding cellulitis is evident at the site flea-bite. The more usual initial lesion is acute inflammation in and d the lymph nodes regional to the site of entry of the organisms. The nodes emorrhagic and surrounded by oedematous haemorrhagic cellular tissue. *tis* are numerous in and around the infected nodes. This regional lymphaathy is the basis of the clinical description 'bubonic plague'.

ns of a haemorrhagic septicaemia are seen in all fatal cases with subrdial and meningeal haemorrhages. There may be haemorrhagic foci of lidation in the lungs, enlargement of lymph nodes and spleen and multiple necrotic foci in the liver. In some severe cases there may be little or no ing of regional lymph nodes; these are the cases clinically presenting as caemic plague'. In deaths from 'pneumonic plague' the signs are those ute congestion in one or more lobes of the lungs and evidence of generalised orrhagic septicaemia. Patients treated with antibiotics may develop pulary abscesses before recovery takes place. *Y. pestis* are numerous in all ted organs.

inical Features. The incubation period is short, three to six days, but less eumonic plague.

BONIC PLAGUE. The most common site of the bubo, made up of the swollen h nodes and surrounding tissue, is one groin but, according to the site of biting by the flea, the bubo may instead be axillary, cervical, epitrochlear opliteal. The onset is usually sudden with a rigor, high fever, dry skin severe headache. Soon aching and then also swelling at the site of the ted lymph nodes begin. Some cases are relatively mild but in the majority of toxaemia rapidly increase, with a rapid pulse, dilated heart and with tal confusion. The spleen is usually palpable.

PTICAEMIC PLAGUE. Those not exhibiting a bubo usually, but not invariably, iorate rapidly if not treated. Pneumonia and expectoration of blooded sputum containing *Y. pestis* may complicate bubonic or septicaemic ue.

PNEUMONIC PLAGUE. The onset is very sudden with cough and dyspnoe
patient expectorates copious blood-stained frothy, highly infective s
becomes cyanosed and rapidly deteriorates. Moist sounds are heard
lungs but there are no signs indicating consolidation.

Diagnosis. Early diagnosis is urgent. A report of deaths among rats
human infection should alert all medical personnel. Especially under
circumstances a bubo, with no evident local pyogenic cause for it, mu
punctured, using a dry syringe and needle. Staining a smear of the as
with methylene blue will show the characteristic bipolar appearance
organisms. For confirmation the aspirate or blood can be cultured. A
cytosis distinguishes 'septicaemic plague' from typhoid fever; blood cult
usually necessary to establish the diagnosis although occasionally the orga
can be seen in a stained blood film. The sputum of a patient with pneum
plague contains very numerous *Y. pestis*. Serological tests show incre
titres of antibodies in convalescence. Plague is notifiable under the I
national Health Regulations.

Treatment. Streptomycin is the drug of choice in the treatment of pl
The first dose should be 1 g intramuscularly, followed by 500 mg ever
hours until the temperature has been normal for 24 hours, after which
should be given daily for a further six days. Excellent results have been achi
with this course of treatment, especially when it is started early in the dis
Tetracycline has proved to be almost as effective as streptomycin: the in
dose should be given intravenously. The adult oral dose is 1 g every six h
for 48 hours or longer, depending on the response. After improvement the
is reduced to 2 g daily and continued for a further 14 days. If no antibio
available, intensive treatment with a sulphonamide should be given. In p
monic or severe septicaemic plague a combination of tetracycline and stre
mycin is recommended, administered intravenously if necessary. Local treatm
of buboes by the application of glycerine gives considerable relief. The b
should not be incised unless it points. With antibiotic treatment it is uncomn
for suppuration and ulceration to develop.

Personal Prophylaxis. There are two main types of vaccine, the killed vacc
given in two or three doses, and a vaccine containing live avirulent organis
requiring one dose only. The latter has been used with success among indigen
peoples but the killed vaccine is still widely used. Its administration is oft
followed by a considerable toxic reaction. The immunity conferred is enhanc
by revaccination after three to six months. Live avirulent vaccine also usua
causes fever, which may last for 5 to 10 days.

Against bubonic and septicaemic plague prophylaxis largely depends
preventing infection by fleas carrying plague. This can be achieved in t
case of the domestic rat by preventing its access to food and by the use
bait containing a poison such as warfarin (an anticoagulant) or bariu
carbonate.

Residual insecticides have revolutionised anti-flea measures. Dusting wi
insecticides and immunisation by vaccine afford good protection. Powde

ning 1·5 per cent Dieldrin or 2 per cent Aldrin applied to floors and into rat holes kill all the fleas and remain active for 9 to 12 weeks. The cide chosen should be one to which the local fleas are known to be tible.

tacts should be protected by tetracycline or by intramuscular strepto- . 1 g daily for a week, or if this is not available, a sulphonamide such as dimidine 3 to 6 g daily for the same period. Those attending on patients neumonic plague should in addition wear masks, protective gowns and .

TULARAEMIA

laraemia is an infection due to *Yersinia tularensis* transmitted to mammals irds by the bites of infected blood-sucking flies and ticks. Man may be entally infected in a laboratory or while skinning infected wild rabbits res. In Norway lemmings are another source. The micro-organisms enter gh dermal abrasions, the conjunctiva or mouth. Contaminated water, ted meat and the bites of infected arthropods may also convey the infection an.

ographical Distribution. The disease is found in the United States, Canada, ico, Japan, USSR, Scandinavia and most European countries.

thology. Focal areas of necrosis occur especially in lymph nodes, spleen, , kidneys and lungs. There may be cutaneous, oral or ophthalmic lesions n infection is by these routes.

linical Features. The incubation period is from 1 to 10 days. There is a den onset of high fever followed by sweating and prostration. After some y remission of the fever, the temperature rises again after a few days and ains elevated for 10 to 15 days but in severe infections there may be no y remission and the fever may last continuously for three or four weeks. re is a moderate neutrophil leucocytosis. The spleen is sometimes palpable. out two days after the onset a primary lesion develops in the conjunctiva ne eye or in the skin at the site of an abrasion if the organisms have entered his way. Such a site is swollen and painful and accompanied by swelling he regional lymph nodes. When the mouth has been the portal of entry a cal ulcer or inflamed tonsils may be found. Pleuropulmonary and peri- dial inflammatory lesions result from inhalation of the organisms or from matogenous spread. Lymph nodes may remain enlarged for months.

iagnosis. The organism may be cultured from the blood although often after repeated attempts. Guinea-pig inoculation may succeed. An intra- nal test using killed *Y. tularensis* may be positive as early as the third , followed by positive agglutination and complement-fixation tests after 10 2 days. Antibodies produced by brucellae may also agglutinate suspensions *. tularensis.*

Treatment. Most cases respond rapidly to intramuscular streptomycin daily. In severe cases the drug should be continued for two weeks. The organ is usually also sensitive to tetracycline.

Prevention. Masks should be worn in the laboratory and gloves should used when skinning rabbits and hares in endemic areas. Adequate cook renders infected meat safe for eating.

CHANCROID

(SOFT SORE)

This is an important and common venereal disease of the tropics, presenti usually in males since the condition in females is asymptomatic, and diffic to recognise. The causative organism, *Haemophilus ducreyi*, a Gram-negati bacillus, is 1 to 2 microns in length and is seen in pairs, chains or arrang like fish in shoals. Invasion of the lesions by pyogenic organisms is common.

Clinical Features. The incubation period is two to three days, but ma occasionally be longer. The initial lesion is a small red papule on the mucou or skin surfaces of the genitalia or on the surrounding skin. In a few days painfu necrosis, ulceration and purulent discharge appear, and a well-demarcate surrounding zone of erythema develops. Frequently the lesions are multipl from auto-inoculation and are seen in all stages of development. The inguina lymph nodes may enlarge, soften and suppurate. General malaise and feve may accompany the local signs.

Diagnosis. Differentiation is required from syphilis, lympho-granuloma inguinale, granuloma venereum and genital herpes. Scraping or aspiration of material from the lesion may reveal the *Haemophilus* which is, however, often overgrown by secondary invaders. Aspiration of a bubo may be more successful. Auto-inoculation of fluid from the lesion on the scarified forearm produces a swelling in which biopsy will demonstrate a recognisable histology. A skin test using a commercial vaccine (e.g. Dmelcos) is also available. Opinions vary as to the value of the two latter tests.

Treatment. It is vital not to mask or miss associated syphilis; therefore only local cleansing with saline should be undertaken and an oral sulphonamide administered until four dark-ground examinations have failed to reveal *Treponema pallidum*. Thereafter excellent results will be obtained with tetracycline, streptomycin or chloramphenicol. Serological tests to exclude latent syphilis should be carried out three months after the completion of the course of treatment.

YAWS

(FRAMBOESIA)

Yaws is a disease of certain underdeveloped tropical countries where it is still to be found among the more backward indigenous people remote from gressive influences. The cause is *Treponema pertenue*, morphologically stinguishable from the causative organisms of syphilis and pinta. Sero-cal changes are almost identical with those produced by syphilis. Organisms transmitted by bodily contact from a patient with infectious yaws through or abrasions of the skin of another person, usually a child. Infection is t likely to take place in huts at night when the temperature and humidity high and families use communal sleeping mats.

eographical Distribution. Areas of infection exist in Mexico, Panama, the rthern parts of South America, West Indies, Central, East and West Africa, Pacific Islands, Malaysia, Burma, Thailand (uncommonly in India and Lanka), and also in Indonesia and the Far East, including China where it ends into temperate zones.

athology. At the site of the inoculation a proliferative granuloma develops taining numerous treponemata. This primary lesion is followed by eruptions, most characteristic being multiple papillomatous lesions of the skin with a tology similar to the primary lesion. In addition there may be hypertrophic iosteal lesions of many bones with underlying cortical rarefaction. All these ions of 'early yaws' heal without appreciable scarring or deformity unless re has been secondary infection. After a variable interval 'late yaws' may velop, characterised by destructive lesions which closely resemble the gum-ta of tertiary syphilis and which on healing produce much scarring and formity.

Clinical Features. The incubation period is three to four weeks. The primary ion or 'mother yaw' is usually on the leg or buttocks and may arise at the e of contact when a child is carried by an infectious adult. The secondary uption usually follows a few weeks or months later, sometimes before the imary lesion has healed. The most typical are the so-called papillomata, often ry numerous, consisting of exuberant tissue covered with a whitish-yellow udate, and more prolific in the moist flexures and around the mouth. There ay be successive crops of lesions. In spite of an eruption of a formidable pearance, the subject, usually a child, is not in a toxic state but may be tive and relatively unconcerned except for the irritation caused by the sores d the attentions of the flies which they attract. These lesions are highly ntagious. Sometimes a pathologically similar lesion erupts through the palm r sole, when walking becomes painful. The resultant gait has given rise to e description, 'wet crab yaws' which may also be produced by more diffuse yperkeratotic lesions with cracks in the skin. The bones of all the fingers istal to the carpus, except the terminal phalanges, particularly in children, ay rarify and be surrounded by periosteal deposits. The swollen fingers are en aptly described as resembling sausages. There may be a similar swelling f a long bone and also of the nasal bone (goundou). The distorted tibia may emain as the sabre tibia but most of the lesions of early yaws will eventually ubside almost completely and spontaneously. Healing is much more rapid fter the administration of penicillin. Other lesions of early yaws include a ariety of cutaneous eruptions, synovitis and diffuse ganglia.

LATENT YAWS. Following the spontaneous resolution of 'early yaws' se logical changes may persist, to be followed by further manifestations of 'ea yaws' or, after an interval of as much as 5 to 10 years, by the tertiary lesi of 'late yaws'.

LATE YAWS. Solitary or multiple nodular lesions may develop. They so ulcerate and spread superficially and also, in places, penetrate deeply in the underlying tissue. In this way gross disfigurement may be caused with d tressing ulceration and deformity. There is some evidence that the site development of late yaws may be influenced by sensitivity to local reinfecti with treponemata. Thus a mother with latent yaws, nursing a child with ear yaws of the face, may develop a tertiary ulcer on the breast. The lesions late yaws tend to heal with scarring in one part even while the ulcer is extendi in another direction. In addition, in radiographs, localised areas of rarefacti may be shown in long bones with surrounding periostitis. Clinically the present as localised swellings of bones and the overlying tissue may ulcera giving a picture resembling the gummatous ulceration of tertiary syphili Lesions of a solitary bone in the hand may lead to the destruction of the bon and deformity. Lesions of the scalp and underlying localised osteitis of the oute table of the skull are common. The bones of the nose and palate may shar in this process. Minor degrees of a sunken nasal bridge or palatal perforatio are common and gross mutilation making the nose and mouth one ope cavity 'gangosa' is one of the most tragic results still compatible with life The plight of other untreated patients may also be very pitiful, with distortio of bones, contraction of joints, ulceration and scarring. Other late lesion include hyperkeratosis with fissuring of the palms and soles 'dry crab yaws' hydrarthrosis, bursitis and juxta-articular nodules consisting of painless, firm subcutaneous fibrous deposits about the elbows, hips and knees.

Unlike tertiary syphilis, yaws does not affect the cardiovascular system or internal viscera, and the only neurological changes are very minor alterations of the cerebrospinal fluid.

Treatment. Long-acting penicillin is highly effective. Very good results follow the intramuscular administration of 1·2 mega units of PAM (procaine benzylpenicillin with 2 per cent aluminium monostearate) on two occasions with an interval of one week. For a mass campaign a single dose of 1·2 mega units is given to all active adult cases and 0·6 mega units to latent cases and contacts, which in areas of high endemicity include the whole of the remainder of the population. Proportionate doses are given to children. A second survey and campaign of treatment should follow within a year to detect and treat relapses and missed cases. Tetracycline 1 to 2 g daily for five days is as successful as penicillin, but the cost and technical difficulties of ensuring that the drug is taken daily make it suitable only for the treatment of an individual patient who is under proper control.

Prevention. With improved housing and increased cleanliness the disease disappears. Anti-yaws campaigns with antibiotics should therefore be only part of a co-ordinated plan to improve the economy, education and hygienic litions of the people. In few fields of medicine have chemotherapy and roved hygiene achieved such dramatic success as in yaws.

ENDEMIC (NON-VENEREAL) SYPHILIS

poradic venereal syphilis is usually transmitted by sexual intercourse. In ain tropical countries, where lack of hygiene prevails, a treponematosis urs as a family disease, the lesions of which show a close resemblance to se of venereal syphilis. This condition has been given the local names of *l* in Arabia, *njovera* in Rhodesia, *dichuchwa* in Botswana, *siti* in Gambia *skerljevo* in Bosnia and was known as *sivvens* or *sibbens* when formerly as endemic in Scotland. The causative organisms are regarded as modified ins of *Treponema pallidum*, with which they are morphologically identical. Johns Hopkins International Treponematosis Laboratory has reported ins from patients with endemic syphilis as exhibiting in the laboratory stant biological differences from *T. pallidum* obtained from venereal syphilis l from *T. pertenue* and *T. carateum*, the causes of yaws and pinta respectively.

Congenital infections are extremely rare and it is unusual for the infection be acquired by sexual intercourse. The common mode of infection is through abrasion, the disease being transmitted from one child to another and casionally from a child to a parent. Sometimes it spreads in a closed com- nity by the use of common drinking vessels and possibly, on occasions, chanically by flies. The poor social conditions in which the disease prevails similar to those where yaws is found but the clinical lesions resemble those juvenile syphilis.

In contrast to sporadic venereal syphilis the primary lesion is rarely seen, cept when a child has inoculated the nipple of the mother during suckling. e lesion presents as an ulcerative papule without regional adenitis. The condary and tertiary lesions include all the common types of skin and bone anifestations of syphilis but typical papillomatous lesions resembling yaws e infrequent. In addition, 'mucous patches' in the mouth, due to superficial ceration, are common and are often the first sign of endemic syphilis but ey are very rare in yaws. Visceral and neurological lesions are absent or rare. he usual serological tests give identical results in sporadic syphilis, endemic philis and yaws.

Treatment. The disease responds to treatment by penicillin in the same way sporadic syphilis. In the social conditions in which it is found the treatment choice is usually a long-acting penicillin, e.g. PAM (p. 34). Prevention epends on the development of improved social and economic conditions and e mass treatment of affected communities with penicillin.

PINTA

Pinta is an infection caused by *Treponema carateum*, morphologically indis- nguishable from *T. pallidum* and *T. pertenue*. It is spread in the same way as n-venereal syphilis.

Geographical Distribution. Pinta is endemic in localised areas in Cen and South America and in some West Indian and South Pacific Islands.

Clinical Features. The incubation period is 14 to 20 days. There is a prim scaly papular lesion on an exposed part, usually the leg. The lesion enlar slowly, up to 10 cm in diameter and is surrounded by smaller papules. Regio lymph nodes enlarge and like the primary lesion contain treponemata. T second stage is manifest 5 to 12 months later and consists of a generalis eruption of macules and miliary papules, 'pintids', pinkish and slightly sca Most of these heal but others coalesce and form hyperpigmented patch commonly on the face and exposed parts. The secondary lesions may pers for years and may be accompanied by hyperkeratosis of palms and soles. the tertiary stage the affected patches become atrophic and depigmented ar in some cases extensive white areas result, 'vitiligo'. In the second and tertia stages there are serological changes closely resembling those of syphilis bı pinta does not protect against syphilis, nor syphilis against pinta. Treatme is by a long-acting penicillin, e.g. PAM (p. 34).

THE RELAPSING FEVERS

The relapsing fevers are a group of diseases due to infections by spirochaete of the genus *Borrelia* transmitted by lice or soft ticks. The louse-borne *Borreli recurrentis* infects only man and is not transmitted from a louse to its progeny This disease appears in epidemics when man is living in conditions under which infestation with the human body-louse, *Pediculus humanus corporis*, is frequent and an infected louse is introduced. It may accompany louse-borne typhus fever. The disease is endemic in Ethiopia from where recently recorded epidemics have probably arisen. Epidemics occur in the tropics as well as in cold climates.

Bor. duttoni, the cause of tick-borne relapsing fever, is transmitted by various species of the genus *Ornithodoros*. These ticks may survive for years even under unfavourable conditions. Once a tick becomes infected, it not only remains infected for life but it conveys the infection to its offspring. Tick-borne relapsing fever is thus an endemic disease. The different species of borrelia are morphologically identical.

Louse-borne Relapsing Fever

The borreliae are liberated from the louse when it is crushed during scratching and the same action, prompted by the irritation of repeated bites from lice, inoculates the borreliae into the skin through excoriations.

Pathology. The borreliae live in the blood, where they are abundant in the febrile phases, and invade the liver, spleen and meninges. Hepatitis causing jaundice is frequent in severe infections and there may be petechial haemorrhages in the skin, mucous membranes and serous surfaces of internal organs.

CLINICAL PATHOLOGY. A neutrophil leucocytosis accompanies the febrile period but is replaced by leucopenia in the apyrexial intervals. In the pyrexial es borreliae are demonstrable in the blood between the erythrocytes. mbocytopenia is marked and impaired liver function tests commonly r. The urine frequently contains protein and sometimes there is frank aturia. The cerebrospinal fluid is often under raised pressure with an ase of mononuclear cells; sometimes in severe infections pus cells and eliae may be demonstrable in the centrifuged deposit.

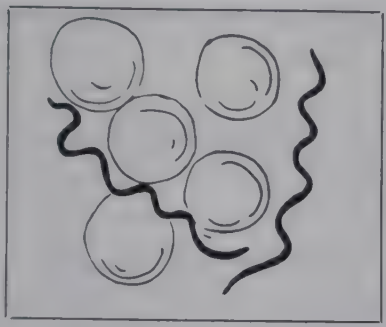


FIG. 4
Borreliae in blood film.

linical Features. After an incubation period varying from 2 to 12 days e is a sudden onset of fever. The temperature rises to 39·5° to 40·5° C is accompanied by a rapid pulse, headache, generalised aching, injected junctivae and frequently epistaxis and herpes labialis. As the disease prosses, the liver and spleen become tender and frequently palpable, jaundice ommon and a petechial rash may appear. Mental confusion and meningism y occur. The fever ends by crisis between the fourth and tenth day, often ociated with profuse sweating, hypotension and circulatory failure. There y be no further fever but, in a proportion of cases, after an afebrile period about seven days there is a recurrence which is usually milder and less longed. Occasionally this relapse is followed by one or two further bouts fever. In the absence of specific treatment there is a considerable mortality, ecially among the elderly and malnourished.

Diagnosis. The organisms are demonstrated in the blood during fever either dark ground illumination of a wet film or by staining thick and thin films. ltural methods may also be used.

Treatment. Tetracycline is effective but may be followed by a Jarisch-erxheimer reaction. The initial daily dose for an adult should not exceed g in four divided doses. In patients in a precarious state, initial penicillin ay prevent a severe reaction to tetracycline. During the apyrexial period 1 g ily should be given for seven days and after a week's interval this course ould be repeated to ensure that there will not be a late relapse.

Personal Protection. The patient and his clothing and all contacts must be ed from lice as in epidemic typhus (p. 60).

Tick-borne Relapsing Fever

This disease, due to *Borrelia duttoni*, is conveyed by a variety of ticks and its demicity is governed by the presence of the vector. In the Mediterranean area

Ornithodoros tholozani is responsible; in the Middle East, Iran, Afghanis and India and in the New World there are other vectors. These ticks can bec infected from rodents or bats as well as by congenital transmission and ma only an incidental host. In Central and East Africa, however, *O. moubat* the vector and man is probably the only important mammalian host. T disease in these areas is thus confined to old camp sites, old houses and th immediate surroundings, infested with *O. moubata* infected from man or congenital transmission. The *O. moubata* lives in dried mud floors and t cracks of the walls of huts plastered with mud.

Pathology. The changes resemble those of louse-borne relapsing fever b with late neurological lesions.

Clinical Features. These are similar to those of louse-borne relapsing feve The febrile bouts, although severe, last usually only for three to five days ar the apyrexial periods may also be shorter. Relapses are, however, more freque and may be as numerous as 10. Iritis and neurological complications, includin cranial nerve palsies, optic atrophy, localised palsies and spastic paraplegi may develop during these later relapses.

Diagnosis. The methods used in diagnosis are similar to those for louse-born relapsing fever. *Bor. duttoni* are, however, scantier in the peripheral blood bu laboratory animals are readily infected.

Treatment. This is the same as for louse-borne relapsing fever.

Personal Protection. Ticks can be killed by lindane (gamma BHC) applied to the inside of the walls and across the entrance to houses.

RAT-BITE FEVERS

There are two rat-bite fevers, one caused by *Spirillum minus*, the other by *Streptobacillus moniliformis*. The latter in addition to being transmitted by a rat-bite has also occurred as an epidemic due to infected milk (Haverhill fever) and in other cases also there has been no known contact with rats or mice.

Geographical Distribution. Both infections are worldwide.

Pathological and Clinical Features. The manifestations of both are very similar. In *Sp. minus* infection (Sodoku) the wound usually heals. After 5 to 21 days it suddenly becomes inflamed, indurated, purplish and painful; it may ulcerate and this stage is accompanied by lymphangitis, regional lymphadenitis, leucocytosis, splenomegaly and fever. After a week the local and general reactions subside but recur after a further few days. Periods of fever lasting 24 to 48 hours are followed by a rapid fall of temperature and, without treatment, febrile bouts may continue to recur for weeks and the patient becomes anaemic. A macular or maculopapular dusky red rash, sparse over the trunk xtremities, appears during the febrile phases. In contrast to streptobacillus arthritis is not common.

streptobacillus fever the incubation period is one to five days. The bite lly heals well but occasionally an abscess forms in the wound. Regional hadenopathy is not marked. The general symptoms resemble those of *ninus* infections but there is frequently painful arthritis and it is unusual ave recurrences of fever after the initial bout which only lasts 48 to 72 s. Sometimes painful swollen joints may be accompanied by a remittent suggesting sepsis.

iagnosis. *Sp. minus* can be demonstrated in the exudate from the inflamed or in fluid aspirated from a lymph node, either by examination under -ground illumination or by inoculation intraperitoneally into an uninfected se. Blood similarly inoculated into mice or guinea-pigs will yield *Sp. minus* e peritoneal fluid 5 to 14 days later. The serum yields false positive serocal tests for syphilis. In *Strep. moniliformis* infections specific seroagglutinins demonstrable after 10 days. A titre of 1 in 80 or a rising titre is considered nostic but the serological tests for syphilis are negative. The organism can ecovered from the blood or, more easily, from an effusion into an inflamed t, by culture on media containing serum or ascitic fluid or by intraperitoneal culation of mice.

reatment. Both infections are readily cured by the following antibiotics: icillin, streptomycin and tetracycline.

Diseases due to Viruses and Rickettsiae

DISEASES DUE TO ARBOVIRUSES

In addition to rabies and the cosmopolitan diseases such as poliomyeli measles, influenza and smallpox, transmitted by direct contact, faecal co tamination, or through the air, there are, in the tropics, a large number viruses pathogenic to man which are arthropod-borne, known by the abbre ation 'arboviruses'. The majority give rise to a febrile illness of brief duratio following which there is partial or complete immunity against further attack Some, in the non-immune, may on occasions be neurotropic, giving rise encephalitis of varying severity. Others, notably yellow fever, may show viscer tropic activity, although it is now recognised that many mild cases of yello fever occur without appreciable impairment of hepatic or renal function.

On recovery from a viral illness immune antibodies are demonstrable in th sera.

Arboviruses are divided on the basis of their antigenic behaviour into group

Group A. In this group are included the viruses of Eastern, Western an Venezuelan equine encephalitis; Chikungunya, O'nyong-nyong and Semlik Forest fevers. All these are conveyed by mosquitoes.

Group B. This group includes the viruses of yellow fever, dengue, Japanes B encephalitis, West Nile, St Louis and Murray Valley fevers conveye by mosquitoes, and those of Kyasanur Forest disease, diphasic meningo-encephalitis, Russian spring-summer fever, louping-ill and Omsk haemorrhagi fever, conveyed by ticks.

Group C. This group now comprises a number of viruses limited to South America.

The remaining arboviruses are placed in a number of small groups or are at present ungrouped. Of particular importance are the viruses causing sandfly fever (p. 45). Haemorrhagic fever with renal syndrome (formerly called epidemic haemorrhagic fever) is now known to be conveyed to man by aerosols from infected rodents so can no longer be regarded as an arbovirus (p. 48). Argentine and Bolivian haemorrhagic fevers are similarly acquired (p. 48).

There are over 60 arboviruses known to affect man. Within each group viruses produce certain antibodies common to other members of the same group. This is of considerable interest as there is evidence that after several attacks by members of the same group there may be protection against the remainder. This phenomenon may contribute to yellow fever being often mild or subclinical among the indigenous people of an endemic area.

Although the clinical manifestations in an endemic area may be sufficiently characteristic for a fairly reliable diagnosis to be made of such diseases as r, sandfly fever and Kyasanur Forest disease, a certain diagnosis rests he isolation of the virus in the early stage of the disease by inoculation oratory animals or fertile eggs, or by the demonstration of a significant se in titre of antibodies in sera taken during and after the illness. Mouse-tion tests were formerly used for this purpose but haemagglutination ion or complement-fixation tests are now employed. Moderate increases presence of antibodies in a single specimen are not diagnostic of an lual virus since antibodies may be common to a group of viruses. Thus esence of antibodies to the viruses for dengue I and II in the sera of forest ls does not necessarily indicate that they are a reservoir of infection, as antibodies may have been provoked by other viral infections.

e accurate elucidation of an infection requires the assistance of a specialised atory to which blood and sera should be sent in a thermos flask packed ce. The identification of the virus may be a laborious and lengthy procedure ay prove to be of extreme importance, as for example, when the outbreak asanur Forest disease was differentiated from yellow fever.

evention of diseases due to arboviruses at present rests mainly on the ol of the vectors, but an efficient vaccine against yellow fever is available. ough the incidence of encephalitis is not great, a composite vaccine to ect against such a catastrophic illness would be a boon but is a far-off pect. At present there are no drugs which are effective against these viruses, he clinical features may on occasion be mitigated by good nursing and ptomatic treatment.

he more common diseases due to arboviruses are dealt with in the section h follows.

YELLOW FEVER

he virus of yellow fever, belonging to Group B of the arboviruses, is trans-ed to man by the bite of an infected Aedes mosquito. The virus is in man's od for two days before the onset of fever, for the first four days of the r and exceptionally for longer. The mosquito becomes infective for man o 20 days after ingesting blood containing the virus and remains infective its life which may be as long as seven months.

pidemiology. Yellow fever is a human disease but there is also a reservoir nfection in primates and other forest animals. In urban areas the vector *ledes aegypti* and here it is a disease limited to human beings, the virus ng conveyed from man to man by this mosquito. *A. aegypti* breeds in small ections of water in the vicinity of human dwellings which are also inhabited the adult mosquitoes. Urban yellow fever is endemic especially in Western Central Africa, but the areas where it is a risk are much more extensive, tching from the Atlantic Coast south of the Sahara to the Red Sea and ian Ocean, and south to Angola and Zambia. Yellow fever is also endemic he jungles of Panama and South America with the exception of Uruguay Chile. In forests the virus is conveyed between monkeys by mosquitoes ng among the tree tops. Man becomes infected by felling trees and being en by these mosquitoes. In Africa monkeys may raid plantations near to forests and *Aedes simpsoni*, present in these rural areas, may become inf by biting the monkeys which are carrying the virus, and later man may be b by these mosquitoes. Life-long immunity is conferred by an attack of disease and babies born to immune mothers are protected for two to months. From the rarity of overt disease among indigenous people in end areas and from serological studies it appears that many acquire immunity f subclinical infections with this and other related arboviruses (p. 40).

Pathology. The main lesions are found in the liver and kidneys but hae rrhages take place into many organs. If the disease has not been rapidly f the tissues will be jaundiced at post-mortem. The liver is often norma size. Degenerative changes in liver cells are widespread but maximal in mid-zonal region where fatty degeneration is intense. Usually refractile aci philic bodies, 'Councilman bodies', may be seen as the result of hyaline degene tion of parenchymal cells. With the high power of the microscope an aci philic intranuclear mass may be detectable, the 'Torres inclusion body'. addition to haemorrhages under the capsule, the kidney shows the changes acute tubular necrosis.

Clinical Features. The incubation period is from three to six days. Leucoper lasts throughout the illness. A mild attack, which is the usual clinical ma festation of the disease in local inhabitants, consists of a short fever acco panied by proteinuria, with little or no jaundice. In those who have no pr immunity the classical attack falls into three phases, the initial fever, a peri of calm and a subsequent period of reaction or intoxication. In very seve attacks the third stage is reached without the brief apyrexial calm interva Virus activity ceases at the end of the first stage, the pathology and clinic features of the third stage being the result of hepatic and renal dysfunctio which are the usual causes of death in yellow fever. The onset of the fever sudden, sometimes with a rigor. There are severe supraorbital headaches, back ache and pains in bones. The face is flushed, the conjunctivae injected an the tongue is coated and the edges are red. These symptoms and signs resembl those of a severe attack of dengue. The patient soon becomes prostrated vomiting may be pronounced and the vomit may contain bile or altered blood If vomiting persists the prognosis is grave. There is increasing epigastric pain mental irritability and photophobia. The fever is highest on the first day and then declines. The pulse rate falls more quickly than the temperature, and bradycardia is marked by the third day. This disproportion between pulse and temperature is very characteristic and is known as Faget's sign. The urine contains protein in increasing quantities and, later, casts appear and the volume of urine decreases. At the end of four days the temperature reaches normal and the second stage, the period of calm, is reached. In mild cases recovery may now take place without further fever. In more serious cases the third stage, the period of intoxication, follows after a few hours, the temperature rising but the pulse still remaining slow. Jaundice becomes pronounced and the liver palpable and tender. The urine contains bilirubin and red cell casts. There is bleeding, sometimes profuse, from gums, nose, stomach, intestine and urinary tract; petechiae, and conjunctival haemorrhages and ecchymoses in the skin pear. The patient remains mentally clear and anxious until near death, only briefly preceded by coma. The pulse rate increases rapidly in the zes. In fulminating infections the patient dies within a few days of the Death rarely occurs in those who survive for 12 days. In some outbreaks o-encephalitis has been a prominent feature. In non-fatal cases conice is without incident and there is no residual detectable damage to neys, liver or heart.

nosis. In an endemic area fever, leucopenia and proteinuria with or t jaundice should suggest the possibility of yellow fever. Blood, sent in ly stages to a laboratory equipped to investigate viruses, may yield the nd tests on sera taken early and late will show the presence of increasing dies (p. 41). These results will only be of value in making a retrospective sis, which may, however, be important on public health grounds. Similarly ablishing of the cause of death by histological examination of the liver e of the utmost importance. The disease is notifiable under the Interal Health Regulations.

erential Diagnosis. Mild cases closely resemble dengue or sandfly fever. with jaundice and proteinuria in the tropics may be due to severe falci- malaria, to blackwater fever or, if there is a leucocytosis, to leptospirosis apsing fever, pyogenic infections such as pneumonia and rarely to an bic abscess of the liver. In infective hepatitis there is no leucocytosis but er usually subsides as the jaundice appears, there is little, if any, proteinuria ne stools may become the colour of clay.

ment. There is no specific antiviral agent. The patient should be nursed a mosquito net for the first four days of the illness. When vomiting is lesome dehydration should be corrected by intravenous glucose saline and transfusions should be given if blood loss is severe. Acute renal failure d be treated (p. **610**).

rsonal Protection. A single vaccination with the 17 D nonpathogenic strain rus, available at internationally recognised centres, gives full protection least 10 years, the period of validity of the vaccination certificate. Ten after vaccination adequate antibodies are present in the blood and the cate of vaccination becomes valid. The vaccine does not produce any ciable side-effects in adults, unless they are allergic to egg protein, when sitisation may be necessary. There is a slight risk of encephalitis following accination of young children, so, if at all possible, vaccination should not rried out in infants under nine months of age. Where vaccination against pox and vaccination against yellow fever are required within a short time, days, yellow fever vaccination should precede the smallpox vaccination. interval can then be safely reduced to 14 days for adults for a primary ation against smallpox and to four days for a revaccination. No ill effects as yet been observed from vaccination during pregnancy but it may be to defer vaccination.

Prevention. Only travellers possessing valid certificates of vaccination a yellow fever are allowed to proceed from an endemic area to 'receptive a by which is meant countries free from the disease but in which the pot vectors exist. In this way the disease has not yet entered Asia. As an addit precaution mosquito control of airports should be maintained. The urban di can be eradicated by the abolition of the breeding places of *Aedes aegyp* the use of residual insecticides in houses (p. **970**), and by mass vaccinati endemic areas. If susceptible mosquitoes are present and the virus persis animals in adjacent forests there remains a risk of an outbreak of yellow among the unvaccinated.

DENGUE

Dengue is caused by a Group B arbovirus (p. 40). Six antigenic vari of the dengue virus have been described. The virus is transmitted to man chi by the mosquito *Aedes aegypti*, but other species of this genus are poten vectors of the disease. Man is infective to the vector 18 hours before the t perature rises and for at least three days after the onset of symptoms. mosquito can transmit the disease 8 to 12 days after feeding on a pati suffering from dengue and remains infective for life.

The disease is a risk in many tropical and subtropical countries, especia in coastal areas. It is most prevalent during the hot season when the mosquit are numerous. One attack usually gives immunity for about nine months a after several attacks a considerable degree of permanent immunity is attain Some cross-immunity exists between dengue and other members of the B gro of arboviruses, including the virus of yellow fever (p. 41).

Dengue is not usually a fatal disease but deaths occasionally occur in childr with the haemorrhagic type described in South-East Asia.

Clinical Features. The incubation period is usually five to six days. Th disease varies considerably in its clinical severity. It may be a sharp illness wit marked constitutional symptoms and signs lasting for 7 to 10 days or a milde disease resembling sandfly fever, with a raised temperature for only two o three days. The fever may be preceded by malaise and headache for two day before the acute onset, characterised by considerable pyrexia and intens generalised aches and pains especially severe in the orbital region and aroun the joints. Painful movement of the eyes, photophobia, conjunctival injectio and lachrymation are often features of the disease. Nausea, vomiting an anorexia are associated with prostration, insomnia and depression. In severe cases the temperature may remain elevated for seven to eight days. An afebrile interval lasting 24 to 48 hours may intervene at the end of the third day when symptoms subside temporarily, to be followed, with a recurrence of symptoms, by a further febrile period of a day or two ('saddleback fever'). The pulse rate is often slow compared with the temperature, and bradycardia may continue well into convalescence. Groups of superficial lymph nodes, usually the cervical, may be enlarged, but this is never a marked feature of the disease. Leucopenia is present throughout the illness.

sh may appear, especially during the second febrile period. It is morbilli- ut the colour resembles that of a scarlet fever rash. It usually begins on rsum of the hands and feet and spreads up the arms and thighs to the In some patients the rash may be scanty or absent while in others it is nd may be followed by desquamation.

r the temperature has fallen, depression and prostration often persist onvalescence. It is, therefore, advisable after a severe attack for the to have at least two weeks' holiday, preferably in a cool climate.

e 1956 there has been a series of outbreaks of dengue in South-East Asia, mes in association with the Chikungunya virus, in which the disease een complicated by haemorrhages, with a variable mortality among nous children, but reaching 10 per cent of those ill enough to be admitted pital.

gnosis. This is usually easy in an endemic area when a patient has the cteristic symptoms and signs of dengue. However, mild cases may resemble virus diseases such as sandfly fever, while a severe attack may be mistaken nicteric yellow fever, but the absence of urinary changes will help to entiate it. Malaria is excluded by a careful examination of the blood. ash may resemble to some extent that of measles but the distribution olour are different and the absence of Koplik spots and catarrhal symptoms pful. When haemorrhages occur the disease may be confused with other hemata having haemorrhagic manifestations, particularly smallpox. There number of dengue-like diseases due to other arboviruses (p. 40). The can be recovered from the blood or its presence deduced from increasing in immunological tests on the sera (p. 41). There appear to be no differences e viruses of dengue I and II recovered from patients with and without orrhagic signs.

eatment. There is no specific treatment. The severe pains can be relieved arge doses of aspirin, paracetamol or codeine, without risk of causing ction but methadone may have to be resorted to. Blood transfusions and costeroids are indicated in the haemorrhagic varieties.

ersonal Prophylaxis. The patient is nursed under a mosquito net. Breeding es of Aedes mosquitoes should be abolished and the adults destroyed by cticides (p. **970**).

SANDFLY FEVER

(PHLEBOTOMUS FEVER)

ndfly fever is caused by a small group of closely related arboviruses (p. transmitted by the sandfly *Phlebotomus papatasii* and by other species of genus. No animal reservoir is known. Man is infective to the vector for 24 s before and for 24 hours after the onset of the fever. The sandfly can smit the disease about seven days after biting an infected person and ains infective for life.

This infection is prevalent in islands in and countries around the M ranean and eastwards into India, Burma and China, especially during dry season when the vector is plentiful. Those who have recently arr an endemic area are particularly liable to be affected. Local adults do no from the disease, probably because of immunity acquired by previous inf in childhood. One attack confers immunity for only a few months, so re reinfections are necessary to maintain a protective level. There is no immunity between dengue and sandfly fever.

Clinical Features. After an incubation period, usually of three to four the onset is sudden with a rapid rise of temperature. The symptoms and are very similar to those of dengue (p. 44). The fever, however, is usua shorter duration, up to three days, and there is no rash. Occasionally may be a recurrence of fever after an interval of a few days. Depressio prostration usually persist for some time after the fever has subsided.

Diagnosis. It is extremely difficult in the early stages to distinguish sa fever clinically from dengue, malaria, influenza and other fevers. In an enc area the general course of the illness suggests the diagnosis, but a blood should always be examined to exclude malaria. The virus can be reco from the blood and serological changes develop (p. 41).

Treatment. This is on the same lines as for dengue.

Personal Protection. As the sandfly breeds in cracks and crevices, it is diff to eradicate it. However, a campaign using insecticides against adult sand can be very effective and this, combined with the use of repellents, gives us protection. The ordinary mosquito net will not keep out the tiny sandfly, a net of very fine mesh which would be effective is difficult to tolerate in weather. Impregnating a mosquito net with an insecticide will, however, pre penetration of the net by sandflies. Modern buildings replacing crumb masonry abolish the breeding places of sandflies.

KYASANUR FOREST DISEASE

The arbovirus of Group B, responsible for this disease, caused a fa epizootic in monkeys in the Shimogo district of Mysore State. It has be shown by immunological tests to affect about 10 per cent of the rural hum population in that area. The vectors are Ixodid ticks of the genus *Haem* *physalis* increased numbers of which had been introduced by the grazing cattle in the area. This disease, first encountered in 1957, is of great inter as it was at first feared to be an outbreak of yellow fever in Asia and illustrat how changing pastoral activities may lead to unexpected outbreaks of diseas

The chief pathological lesions are found in the liver and kidneys.

Clinical Features. The disease in man may be mild with only a short febri attack or it may be a severe illness with fever lasting for over a week wit

rostration and generalised pains in muscles. Mucosal surfaces may
ome patients may relapse after 9 to 21 days when fever and signs of
al irritation may ensue. Jaundice is often prominent. In fatal cases
usually due to liver failure.

ment. The patient requires careful nursing; no specific treatment is
A prophylactic vaccine has been prepared.

JAPANESE B ENCEPHALITIS

virus causing this disease belongs to Group B of the arboviruses and is
itted to man by the bites of infected culicine mosquitoes which probably
d on infected animals or birds, notably nestling herons. Pigs and other
ic animals have been shown to be possible sources of infection but act
as amplifiers of the virus brought to them by mosquitoes. The virus is
read in the Pacific Islands from Japan to Guam, in the Philippines,
n, Borneo, Malaysia and Singapore. In endemic areas, although sero-
surveys indicate a high incidence of subclinical infection, only sporadic
may be encountered. Nevertheless, devastating epidemics, with a high
lity rate, have occurred.

hology. Inflammatory and degenerative changes are found in the brain
which, in a proportion of cases, the virus has been recovered.

ical Features. Many infections are subclinical but overt disease may
at any age, although children are particularly susceptible and not in-
ently die. With the development of encephalitis the patient experiences a
severe headache, fever, often with rigors, and vomiting. The physical signs
ose of meningo-encephalitis, namely, neck rigidity, congestion of the optic
, imperfectly reacting pupils, muscular twitching and tremors; and, in
e cases, progressive coma, muscular rigidity and cranial nerve palsies. In
cases only signs of meningitis are present. The cerebrospinal fluid is under
ased pressure and although there may be no immediate increase of cells
protein in it, this usually develops within a few days. The acute illness
last from a few days to two weeks or longer. Convalescence is prolonged
tedious. Persistent neurological damage is only a feature in children and
prolonged illness in adults. The mortality rate in overt disease varies from
40 per cent.

agnosis. The virus has only rarely been recovered from the blood or
rospinal fluid but in fatal cases may sometimes be obtained from the
. Increasing titres of specific antibodies in the blood is the usual basis for
osis.

eatment. There is no specific treatment and the value of corticosteroids
ot yet been established. Skilled nursing and aids for the patient in coma,
as tracheostomy and artificial respiration, may be life-saving.

Prevention. The elimination of breeding places of the vector mosquit use of larvicides or insecticides, where practicable, should be instituted. is no effective vaccine or other antiviral agent available.

LASSA FEVER

This disease, first observed in 1969, is now known to be due to an aren a group which also includes the viruses responsible for Argentine and B haemorrhagic fevers (p. 40). Recognised outbreaks have so far been limi West Africa, including Nigeria, Liberia and Sierra Leone. The mode of is unknown but case to case transmission in hospital and the presence virus in the pharynx and urine is consistent with inhalation of aeros infection through abrasions. A reservoir of infection has been demonstra rodents by isolation of the virus.

Clinical features. The disease has the general features of a virus infe high fever, intercostal myalgia, bradycardia, a low blood pressure and penia. Adherent yellow exudates on the pharynx are particularly characte The fever lasts between 7 and 17 days. In severe cases shock and elect imbalance develop. Mortality rates of overt infections have varied from cent to 52 per cent but mild and subclinical infections also occur.

Diagnosis. The virus has been isolated in special laboratories from s pharynx, pleural exudate and urine but diagnosis will unusually be estab from 'paired sera', the later specimens being taken 6–8 weeks after the of infection.

Treatment. Isolation and general supportive measures, preferably i intensive care unit, are required. There is no proved specific thera measure. The administration of convalescent immune plasma has been foll by recovery and is therefore recommended for prophylaxis in accid exposure to infection.

HAEMORRHAGIC FEVER WITH RENAL SYNDROME

This disease, formerly called epidemic haemorrhagic fever, is attributab a virus, although confirmation of its successful isolation is still awaited. breaks occurred in Manchuria and Korea and it, or a similar disease, has reported from Scandinavia and Soviet Russia. There is a close associ with small mammals, in particular bank voles, and it has been establi that man becomes infected by aerosols without the intervention of an arthr vector.

Pathology. The main changes arise from increased capillary fragility. there are widespread internal haemorrhages and escape into the tissue fluid rich in protein. Haemorrhages into the anterior lobe of the pituitary he adrenals are common post-mortem findings and in the kidneys acute r necrosis is evident.

ical Features. The incubation period is from 12 to 16 days. The onset den with a temperature of 39·5° C or higher, the face flushed and the ongested. The patient complains of headache, aching all over the body, abdominal discomfort, nausea and vomiting. After about five days the rature falls and the second or toxic stage begins. Haemorrhages now place into the skin and from mucous membranes. The urine contains red casts and a large amount of protein. There is a danger of oliguria and a. With the onset of the second afebrile stage prostration increases and may be severe hypotension. The leucocyte count, low in the early stages, w much increased, at first with primitive granulocytes and later with tive lymphocytes, the picture resembling that of leukaemia. The coagula- and prothrombin times are normal, the platelet count is diminished and is a prolonged bleeding time. Death may ensue in this stage but in favour- cases the third or convalescent stage begins towards the end of the second , with a plentiful flow of urine of low specific gravity, free from protein casts. This polyuria may continue for some months. Full recovery is usual very slow.

agnosis. In an endemic area the diagnosis is suggested by the characteristic cal signs and the successive changes in the blood. Other diseases to be rentiated include leptospirosis, typhus and relapsing fever, thrombocyto- c purpura, leukaemia, haemorrhagic dengue fever and certain other haemo- gic virus diseases described in Russia.

reatment. There is no specific remedy. Rest and careful nursing are essential. y sufficient fluid should be given to maintain the fluid balance. Hypotension be corrected by intravenous plasma or the slow intravenous infusion of a per cent glucose solution in sterile water. Oliguria and anuria are treated dvised for acute renal failure (p. **610**). With prolonged polyuria in con- scence, potassium and sodium losses may require replacement.

KURU

his disease is peculiar to the Fore people, and close neighbours, living in ocalised area of the eastern highlands of New Guinea. The underlying hology is a progressive replacement of nerve cells, chiefly of the cerebellum mid-brain, by gliosis. The symptoms are those of tremor and ataxia, ompanied by emotional instability, with progressive paralysis invariably lting in death, usually within two years of the onset. Children of both s are equally affected but it has only recently been observed over the age 0 years in men and is much commoner in adult females than in young . The age of onset in children, in recent years, has become progressively r, suggesting that no recent transmission of the disease has occurred. An ctive agent, behaving like a 'slow virus', has been transmitted by direct inoculation from the brain of a human victim into the brain of chimpa After repeated passages from brain, liver or spleen of affected chimpa and one race of inoculated spider monkeys the 'virus' now exhibits a incubation period and produces lesions resembling kuru. Kuru thus c resembles 'scrapie', a disease of sheep and goats. It has been postulatec kuru may have been transmitted by the former local custom of womer children ingesting human brain in cannibal feasts, in which men by cu did not partake. Cannibalism declined between 1956 and 1963 when it ce At present this theory seems to fit the observed data better than attrib the disease to a genetic disorder.

No known treatment affects the progressive course of kuru.

LYMPHOGRANULOMA INGUINALE

(LYMPHOPATHIA VENEREUM, CLIMATIC BUBO)

Lymphogranuloma inguinale is caused by a virus of the *Chlamydia* g immunologically related and similar in size to the psittacosis-ornithosis trachoma viruses. They are large viruses and are sometimes included in family of Rickettsiales. The disease is venereal and is widely distributed in tropics, especially in seaports. The virus can be transmitted to monk guinea-pigs and mice, but not to birds, and this readily distinguishes it f the ornithosis virus.

Pathology. The primary herpetiform lesion is small and very superficial. virus passes from the primary lesion to the regional lymph nodes and th causes proliferation of monocytes and lymphocytes and giant-cell forma at numerous foci within the nodes. Untreated, these foci necrose to f multiple small abscesses. Associated with these changes there is a mar connective tissue proliferation in and around the lymph nodes which becc matted together and adherent to the surrounding structures. When the ingu nodes are affected the overlying skin is also inflamed by the periadenitis.

Clinical Features. After exposure to infection one to four weeks elapse bef the evanescent initial lesion appears. In the male this is usually situated on prepuce or glans penis and often escapes notice. Ten to fifty days after expos the adjacent lymph nodes enlarge. In the male in the first stage a single n on one side of the groin is usually affected, but soon other nodes beco inflamed and many become matted together. The infection may spread to other groin and occasionally to the pelvic group of lymph nodes. The affec nodes are tender, and as the disease progresses the large swelling in the ingui region adheres to the underlying tissues and to the overlying shiny purpl skin. Enlargement of the lymph nodes above and below the unyielding inguir ligament produces the characteristic 'groove sign'. With rest and treatme lesions may heal. Otherwise necrotic foci will form and their thick glairy conter will eventually be discharged through the skin by numerous small sinus After this, healing is very slow and often associated with marked scarrir Months may pass before recovery takes place.

he female the primary lesion is seldom found. From the vagina or from ctum of either sex the virus passes to the adjacent lymph nodes in the , and sinus formation will then damage surrounding structures with nely serious and disabling results. Fistulae may form between the rectum, a and urethra, and ulcerative proctitis may cause stricture of the rectum. e female obstruction to the lymphatics may lead to elephantiasis of the al genitalia. These complications in the female constitute the condition l 'esthiomene'.

sociated with the adenitis there may be fever, prostration and loss of t.

agnosis. Material for the intradermal 'Frei' test was originally pus aspirated an inguinal node, but this has been replaced by Lygranum, a viral sus- ion grown on the yolk-sac of the chick embryo. In a positive case 24 hours an intradermal injection of 0·1 ml of Lygranum antigen, a papule exceeding m in diameter will develop and usually persist for two to three weeks. same antigen can be used for the complement-fixation test. Both these tests positive within two to six weeks of the development of the adenitis and in positive for a very long time. As this antigen contains a component mon to ornithosis and trachoma, this must be taken into account in the rpretation of the result.

reatment. To encourage resolution rest in bed is important. Many cases ond well to a sulphonamide, 4 g sulphadimidine daily in divided doses 14 days being a suitable course.

n those resistant to sulphonamides, tetracycline 2 g daily for 14 days often s good results.

he inguinal nodes must not be incised but aspiration, where indicated, may relief. When extensive sinuses have formed, complete excision of the mass nguinal nodes may be required.

or the results of serious lesions arising from pelvic adenitis and for rectal cture surgical aid will be required.

TRACHOMA

rachoma, recognised since the time of Ancient Greece and Egypt, is a cific communicable keratoconjunctivitis, usually of chronic evolution, caused an agent belonging to the *Chlamydia* group of atypical viruses, and charac- ised by follicles, papillary hyperplasia, pannus and, in its later stages, atrisation. The infecting micro-organism is named the trachoma and inclusion junctivitis (TRIC) agent. Young children are particularly vulnerable to ction. Transmission is usually by contact or from fomites in unhygienic roundings. Evidence is accumulating that some infections occur during h from the infected genital passages, TRIC agents of similar serotype ing been isolated from the eyes of a baby, the vagina of the mother and the thra of the father.

Geographical Distribution. The disease is particularly common in the h dusty areas of the subtropics and tropics but is also present in Southern E and among immigrants in Britain. Some hundreds of million people from trachoma. The disease varies markedly in incidence and in sever different geographical areas.

Pathology. The infection lasts for years and may be latent over long pe Recrudescence may result from secondary bacterial infection or fror infection by the agent itself. The conjunctiva of the upper lid is first aff with combined vascularisation and cellular infiltration, pannus, spreadi the upper cornea and later to other areas producing corneal opacity and im ment of vision. Cicatricial deformity of the upper tarsal plate is an feature. Entropion, trichiasis, ectropion and corneal scarring are late resu

Clinical Features. The onset is usually insidious and infection may n apparent to the patient. Early symptoms of conjunctival irritation or sma may be ignored. Watering, stickiness and blepharospasm may be noticed i eyes of children. In underdeveloped areas, unless discovered on surveys. condition may not be reported until vision begins to fail.

The ophthalmic appearances are described in 4 stages (WHO):

STAGE I. Immature follicles are seen on the upper tarsal conjunctiva inclu the central area and early corneal changes are usually present.

STAGE II. Well developed mature soft follicles are present with papil hyperplasia. Pannus and corneal infiltrates extend from the upper limbus.

STAGE III. Some or all of the signs of stage II exist with scarring develop usually from necrosis of follicles.

STAGE IV. The follicles and infiltrates of stage III have been replaced scar tissue and the disease is no longer infectious although further changes the scars may follow. The degree of scarring varies from minimal involvem to trichiasis, entropion, corneal opacities and gross impairment of vision.

Trachoma may also present as an acute ophthalmia neonatorum w secondary bacterial infection.

Diagnosis. Differentiation from inclusion conjunctivitis (blenorrhoea) m be clinically impossible, and in some countries no clear separation can be mad The conjunctivitides of adenovirus, herpes virus and Newcastle disease m closely resemble trachoma. Clinically an early ptosis due to deformity of t upper tarsal plate and appreciation of the characteristic follicular conjunctivi on eversion of the lids may be helpful. Vascularity and cellular infiltratio may be seen using the slit lamp before being visible to the naked eye. Intr cellular inclusion particles (Halberstaedter-Prowazek bodies) are demonstrat in conjunctival scrapings by iodine or immunofluorescent staining. TRIC age may be isolated in the developing chick embryo or in cell culture.

tment. Improvement of the hygienic state is of first importance. Local
lmic ointment or oily drops of 1 per cent chlortetracycline, tetracycline
thromycin may be used twice daily for three months. In mass therapy
emic areas such topical application twice daily for three to six consecutive
ach month for six months has given good results. In some cases daily
cent tetracycline ointment is the method of choice. A systemic sulphona-
daily for three weeks is a useful addition to treatment. Deformity and
ng of the lids, corneal opacities, ulceration and scarring require surgical
nent, after control of local infection.

vention. Personal and family cleanliness should be improved. Proper care
eyes of newborn and of young children is essential. The finding of a case,
ularly in a child, should lead to examination of the whole family. Popula-
urveys should lead to discovery and treatment of asymptomatic infections.
homa clinics are required in highly endemic areas.

DISEASES DUE TO RICKETTSIAE

ckettsiae are small organisms, about 0·5 micron in diameter, and are
ral inhabitants of the cells of the intestinal canal of arthropods. Some
es parasitise higher mammals and are pathogenic to man. Rickettsiae are
mediate between viruses and bacteria and all require living cells for their
iplication. Infection is usually conveyed to man through the skin from
eta of the arthropods but in some vectors the salivary glands are affected
then bites are a mode of infection. Transovarian infection in arthropods
he next generation occurs except with *R. prowazeki* and *R. mooseri*,. the
es respectively of louse- and flea-borne typhus. The Weil-Felix reaction,
ch is the non-specific agglutination by the patient's serum of the strains
rganisms Proteus OX 19 or OXK, helps in the differentiation of the infec-
s. The following table gives the reactions in the human infections:

Name of Disease	Vector	Weil-Felix Reaction	
		OX 19	OXK
pidemic typhus	Louse	+ + +	negative
ndemic typhus	Flea from rat	+ + +	negative
ocky Mountain spotted fever	Tick	+	negative
ther forms of tick typhus	Tick	+	variable
crub typhus	Larval mite	negative	+ + +
(Query) fever	None or tick	negative	negative
ickettsialpox	Mite from mouse	negative	negative
rench fever	Louse	negative	negative

---

though several of these conditions are not found in the tropics they are included here to
plete the group.

Pathology. Rickettsiae are characteristically parasites of the vascular thelium, especially of capillaries and other small vessels, producing lesi the skin, central nervous system, heart, lungs, kidneys and skeletal m Endothelial proliferation, associated with a perivascular reaction (nodu Fraenkel) may cause thromboses and often small haemorrhages. In epi typhus the brain and in scrub typhus the cardiovascular system are partic attacked. A specific pneumonitis is frequent in scrub typhus.

The rash in epidemic, endemic and scrub typhus is at first central, b tick typhus it starts peripherally. In Q fever only a sparse rash is occasi seen. An eschar often shows the site of the bite in tick and scrub typhu in rickettsialpox, but not in epidemic and endemic typhus or in Q fever.

The common clinical findings in this group of diseases are fever, s prostration, mental disturbance and often a rash. The diagnosis can be establ by the Weil-Felix reaction in epidemic, endemic and scrub typhus an complement-fixation and agglutination tests using antigen from the sp *Rickettsiae* in all infections. *Rickettsiae* can be isolated in specialised labora by inoculation of laboratory animals or fertile eggs.

EPIDEMIC TYPHUS

Louse-borne or epidemic typhus caused by *Rickettsia prowazeki* is tr mitted by infected faeces from the louse of man, usually through scratc the skin, but sometimes by inhalation. Patients suffering from epidemic ty infect the lice, and these leave the patient if he is febrile. In conditions of c crowding the disease may spread rapidly. During interepidemic periods disease may be maintained by inapparent or latent cases ('Brill's disease' perhaps by infected fleas and rats.

Pathology. Vascular changes in typhus are especially characteristic in vessels of the brain. There may be increased pressure of the cerebrosp fluid with excess of protein and lymphocytes. The white cell count is usu normal.

Clinical Features. The incubation period is usually 12 to 14 days. Th may be a few days of malaise but the onset is more often sudden with rig frontal headaches and pains in the back and limbs. The temperature rises two or three days, constipation is constant, and bronchitis usually distressi The face is flushed and cyanotic, eyes congested, and the patient soon beco dull and confused.

The rash appears on the fourth to the sixth day and often resembles meas In its early stages it disappears on pressure but soon becomes petechial w subcutaneous mottling. It appears first on the anterior folds of the axillae, si of the abdomen or back of hands, thence on the trunk and forearms. The ne and face are seldom affected.

During the second week symptoms increase in severity. Sordes collect the lips, and the tongue, dry and brown, becomes shrunken and tremulo The spleen becomes palpable, the pulse feeble and the patient stuporous a us. If the patient recovers, the temperature falls rapidly at the end of ond week and convalescence ensues. In fatal cases the patient usually the second week from general toxaemia, heart or renal failure or onia.

mon complications are bronchopneumonia, parotitis, venous thrombosis ngrene.

nosis. The clinical features may be almost diagnostic especially when is an epidemic of the disease. In mild cases of the disease, however, l symptoms and signs may be much less distinctive. In the Weil-Felix glutination of Proteus OX 19 over 1/200 is usual after the seventh day; g titre is of particular diagnostic value. The complement-fixation test killed suspension of *R. prowazeki* gives reliable results and differentiates n flea-borne typhus.

asles, meningococcal septicaemia, malaria, relapsing fever, typhoid fever, pox and other fevers of the typhus group have to be differentiated.

ENDEMIC TYPHUS

a-borne or 'endemic' typhus is caused by *R. mooseri*, which on intraoneal inoculation of a guinea-pig, causes a febrile illness with a marked, haemorrhagic, scrotal reaction (Neill-Mooser reaction). This reaction is ual in *R. prowazeki* infection. Man is infected when, by scratching, he duces the faeces or contents of a crushed flea (*Xenopsylla astia* or *X. is*) which has fed on an infected rat. The incidence of the disease is adic.

thology. Deaths are rare in human infections, so morbid changes, probably ter than in louse-borne typhus, have not been studied in detail.

inical Features. The incubation period is 8 to 14 days. The symptoms mble those of a mild louse-borne typhus. The rash may be scanty and sient.

iagnosis. The Weil-Felix OX 19 is positive as in louse-borne typhus and specific complement-fixation test using *R. mooseri* antigen is positive by ninth day.

TICK-BORNE TYPHUS FEVERS

Rocky Mountain Spotted Fever

he causal organism, *R. rickettsi*, transferred by the bite of ticks, carries ase to rodents and dogs and on occasion to man when brought into contact these animals. It is widely distributed in western and south-eastern States ne USA and also in South America.

athology. The vascular changes are similar to those in epidemic typhus. ddition, haemorrhages and gangrene of the genitalia, ears and digits sometimes occur and there may be bronchopneumonia and enlargement spleen and liver.

Clinical Features. The incubation period is about seven days. There r an eschar at the site of the bite, with enlargement of the regional lymph Symptoms, which include severe headache, generalised pains and high falling by lysis during the third week, closely resemble those of louse typhus. The rash appears about the third or fourth day, at first like m but in a few hours the typical maculo-papular eruption appears. Lesions red at first, become fainter with the morning remission of fever in the stages. Each day, however, they become more distinct and papular unti are petechial. The rash first appears on the wrists, forearms and ankles, sp in 24 to 48 hours to the back, limbs and chest and lastly to the abdomen it is least pronounced. The fully developed rash often affects also the p soles and face. Petechiae may appear in crops. Cutaneous and subcuta haemorrhages of considerable size may appear in severe cases. Complica are as in louse-borne typhus. Untreated, the course of the disease may be or rapidly fatal.

Diagnosis. There may be a history of a bite by a tick. The character o rash, appearing first at the periphery, is helpful. The rickettsiae can be isc from the blood (p. 54). The Weil-Felix reaction is not of much help. Agglu tion and complement-fixation tests using *R. rickettsi* antigen are positive i second week.

Other Forms of Tick-borne Typhus

The causal agents of African tick-borne typhus are *R. conori* and a subs *R. conori pijperi*. They cause typhus in South and East Africa, the rese hosts being dogs and rodents. 'Fièvre boutonneuse' of the Mediterrane similar, as is also the infection in Queensland where *R. australis* is the ca organism. There are antigenic differences between these various rickettsiae eschar and lymphadenitis are usual. The rash is maculo-papular and may c the trunk and limbs and affects the palms and soles. There may be delir and meningeal signs in severe infections but recovery is the rule except in debilitated. There are no haemorrhages into the skin. Positive results obtained in the Weil-Felix test in the majority of cases but may be only to a titre.

The infection may be acquired by walking on grasslands but in ende areas dogs may bring the infected ticks into the house.

SCRUB TYPHUS

Mite-borne or 'scrub' typhus is caused by *R. tsutsugamushi* transmitted the bite of infective larval mites, such as *Leptotrombidium* (*Leptotrombidi akamushi* and *L.* (*L.*) *deliense*.

Geographical Distribution. Far East, Assam, Burma, Pakistan, Indone S. Pacific Islands and Queensland.

ogy. This is similar to that of louse-borne typhus, but lesions in the e more prominent. A primary eschar and necrosis of the superficial the dermal epithelium are correlated with mononuclear infiltration, and intimal changes at the site of the bite.

al Features. The incubation period is about nine days. In most cases r, starting as a small papule, becomes a small rounded or oval ulcer mm in diameter surrounded by a red indurated area. Multiple eschars not infrequently. The associated lymph nodes are often enlarged.

nset of symptoms is usually sudden with headache, often retro-orbital, alaise, weakness and cough, occasionally with diarrhoea. The con- e become injected. In severe cases the general symptoms increase, with nd prostration. A rash often appears on about the fifth to the seventh first reddish macules on the front and back of the chest and on the nal wall. In twenty-four hours it becomes a raised maculo-papular hich soon appears on the face, neck, arms, palms, legs and soles. The ually fades by the fourteenth day. The temperature rises rapidly and es as a remittent fever with sweating until it falls by lysis about the to the eighteenth day. The fever and rash are frequently associated neralised enlargement of lymph nodes which are firm, elastic, discrete nless.

h and headaches are troublesome and mental change may be striking. tenth day the patient is prostrate, lethargic and querulous, distressed h and often deaf. The pulse, slow at first, becomes rapid in severe cases, ripheral circulatory failure frequently precedes death. There are often f pneumonitis, especially towards the bases of the lungs. The sputum e frothy and streaked with blood. Radiological changes in the lungs, present, are similar to those found in virus pneumonia. In patients ssing to recovery the temperature falls by lysis, but convalescence is low and tachycardia may persist for some weeks. Mild cases show less symptoms and recovery is quicker.

gnosis. In endemic areas diagnosis is often possible on the clinical findings r, severe headache and congested conjunctivae. An eschar, rash, enlarged nodes and mental changes give further assistance.

eric fever, malaria, leptospirosis and other forms of typhus must be ed.

ation of rickettsiae by intraperitoneal inoculation of blood into mice the first week is diagnostic. The Weil-Felix reaction with Proteus starts after the seventh day and reaches a maximum two weeks later. lement-fixation and agglutination tests using *R. tsutsugamushi* antigen sitive after the second week.

Q (Query) FEVER

causative organism of this disease, which occurs throughout the world, sufficiently from other rickettsiae to be placed in a separate genus and is known as *Coxiella burneti*. Ticks of several genera are vectors of C. and these convey the infection to many wild animals and to large c animals. These organisms are very resistant to drying and so lend the to dissemination by air. Man may become infected by inhaling or i infected dust, rarely, if ever, by the bite of a tick. Dried genital dis milk and urine from infected animals appear to be important sou infection amongst meat handlers and agricultural workers. Infected str other packing material have also been incriminated. Infections hav acquired in laboratory and autopsy rooms.

Clinical Features. The incubation period is 7 to 14 days. The onset is with fever, sweating and general malaise, cough, retro-orbital pain and ar The temperature rises from 39° to 40·5° C with daily remissions, to normal after 4 to 15 days. The pulse is slow, prostration often marked dry cough is often present about the fifth or sixth day with scanty s occasionally bloodstained. Pains in the chest are frequent, but physic are minimal—perhaps a few fine crepitations and slight dullness on perc The spleen is sometimes palpable and occasionally a sparse rash is p Radiographs show patchy homogeneous ground-glass areas of consoli single or multiple, usually towards the base of the lungs. These usually in about ten days. Occasionally the lung fields show no radiological c Hepatitis, encephalitis and endocarditis with features resembling ba endocarditis are rare complications.

With the fall of temperature convalescence is usually rapid and comp

Diagnosis. The clinical symptoms resemble those of virus pneumonia septicaemia. The Weil-Felix test is negative but, with a specific antiger *C. burneti*, antibodies can be demonstrated in the second week and are m in the fifth or sixth week. The organisms can be recovered from the (p. 54).

RICKETTSIALPOX

This disease is due to *R. akari*, transmitted from the domestic mouse mite. It appears to be restricted to New York and Philadelphia where mi now adapted to live in communal rubbish chutes of apartment houses.

Pathology. The lesions in the skin show necrosis of the capillary walls thrombosis, perivascular lymphocytic infiltration and small haemorrhage lesions of other tissues have been observed, and the leucopenia is modera

Clinical Features. The first lesion starts as a deep-seated papule w gradually enlarges to form a rounded or oval vesicle. This eventually sh to a black eschar which separates after one to two weeks. The regional ly nodes are usually enlarged.

About a week after the appearance of the first lesion fever, sweating and h ache begin quite suddenly and continue for about a week.

The typical rash appears within the first four days of the fever. The le maculo-papules later forming vesicles at their centres. They soon dry black crusts which are shed after a few days leaving no permanent here is no special site for the lesions, but they avoid the palms and e patient is never seriously ill.

osis. The rickettsiae can be isolated from the blood during the acute . 54). The complement-fixation test with *R. akari* is positive.

TRENCH FEVER

h fever is caused by *R. quintana* and is spread to man by louse faeces. prevalent in the First World War in the trenches when troops were us and again in the Second World War in the USSR.

logy. The disease is not fatal so the pathology is not well documented. s in the skin include hyperaemia, oedema and perivascular cellular ion without any typical vascular lesion.

cal Features. The incubation period is 10 to 20 days. The onset is sudden adache, severe pains in trunk and limbs and tenderness in the back and pecially in the shins. The temperature rises sharply and remains consly raised for five to seven days. Occasionally the fever is intermittent. relapses are common, usually at intervals of five to six days. Three to ch bouts may be expected. Tachycardia may be a feature. A rash, usually r but occasionally papular, distributed mainly on the trunk, may appear second day of the fever and last only one day. It is rose-red early and ecomes a dull red. The spleen is usually palpable. In chronic relapsing atigue is often marked and convalescence may be prolonged for several s.

gnosis. In the presence of an outbreak the clinical picture of pains, rash brile relapses should suggest the diagnosis of trench fever. In addition er rickettsial diseases, enteric fever, malaria, relapsing fever and brucellosis be excluded.

Treatment of the Rickettsial Diseases

cific Treatment. The various fevers due to rickettsiae vary greatly in ty but all respond to broad-spectrum antibiotics. Chloramphenicol was st to be used and was dramatically successful. The typhus group, however, nd very well to tetracycline and, as aplastic anaemia is an occasional lication from chloramphenicol, it is wiser to use tetracycline. It is used standard dose, for an adult, of 250 mg four times daily, but on the first ouble this dose may be given. In severe infections the dose is 500 mg four daily for the first three days. The fever usually settles within two or three As the action of tetracycline is mainly bacteriostatic, there is a tendency apse and it should, therefore, be continued for five to seven days after the t is afebrile.

General Management. The patient suffering from louse- or fl typhus is a danger to others unless he has been disinfested.

When the temperature is high, sponging gives great comfort; fo pyrexia, i.e. over 41° C sponging with cold or iced water is required. If h is intense and fails to respond to aspirin or codeine, lumbar punctur be performed to relieve the increased intracranial pressure and to de concomitant bacterial meningitis. Delirium may need to be contro sedatives while awaiting the effects of specific chemotherapy.

In scrub typhus pneumonitis may be a serious feature, and oxygen needed.

Convalescence is usually protracted especially in older people.

Prophylaxis. In louse- and flea-borne typhus and in trench fever steps be taken to get rid of all lice and fleas and their faeces. An insecticide can be insufflated into the undergarments of those at risk without their u ing. To prevent flea-borne typhus food stores and granaries should be pr from rats. Rats and their fleas must be destroyed.

Attendants on patients with louse-borne typhus should wear pro clothing smeared with an insect repellent such as dimethylphthalate (The patient should be washed, and an insecticide powder applied al especially to the hairy parts. His clothing should be immersed in disin before being sterilised.

To guard against tick-borne typhus dogs should be regularly disinfe ticks with forceps and should not be allowed to sleep in bedrooms. Pro of the legs when walking through grasslands may reduce the risk of p up infected ticks. The early removal of ticks and cleansing the site of th are also important.

Mite-borne typhus is acquired when man enters scrub country in en areas. Protection against the larval mite can be secured by wearing su clothing, the inside of which has been smeared once a week with a mite-rep such as DMP. Mites can be destroyed by aerial spraying of infected with Aldrin or Dieldrin, repeated every three months.

ACTIVE IMMUNISATION. Those likely to be at risk can be protected a louse-borne and flea-borne typhus by Cox's vaccine prepared from cultures of strains of *R. prowazeki* and *R. mooseri* cultured in eggs. doses each of 1 ml should be given subcutaneously at intervals of 7 to 10 and when the risk is grave booster doses of 1 ml should be given at six-mo intervals. Cox's vaccine against infection with *R. rickettsi*, similarly pre and administered, gives good protection. To maintain the immunity the cinations should be repeated annually.

So far no protective vaccine is available against mite-borne typhus.

ses due to Helminths

SCHISTOSOMIASIS (BILHARZIASIS)

e three species of flukes of the genus *Schistosoma* which commonly ease in man, *S. haematobium*, *S. mansoni* and *S. japonicum*. *S. haema-* as discovered by Theodor Bilharz in Cairo in 1861 and the disease mes called bilharziasis and the genus, *Bilharzia*. Certain other species, *latum*, *S. bovis* and *S. matthei* relatively rarely affect man. When the assed in the urine or faeces and gains access to fresh water, the ciliated m inside it is liberated and, if a suitable freshwater snail (p. 67) is , it soon penetrates this intermediate host. In the snail in the hot

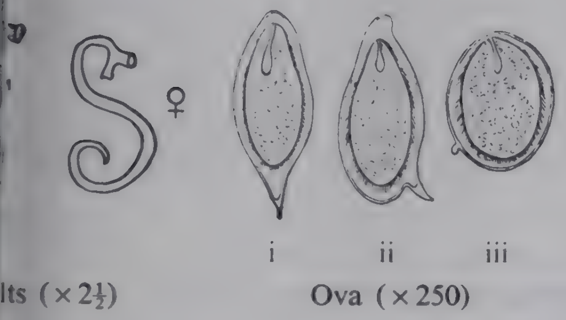


FIG. 5
Schistosoma.
i. *S. haematobium*, ii. *S. mansoni*,
iii. *S. japonicum*

t develops into large numbers of fork-tailed cercariae which are then d into the water where they may survive for one to three days. These e can penetrate the skin if there is only a thin film of water next to it, mucous membrane of the mouth of their definitive host, man; after to the lung they migrate to the portal vein where they reach maturity. le worm is up to 20 mm in length and the more slender cylindrical usually enfolded longitudinally by the male, is rather longer. Within six weeks of infection they migrate to the venules draining the pelvic where the females deposit their ova. Whereas the eggs of *S. haematobium* l chiefly in the walls of the bladder and rectum, the eggs of *S. mansoni* *japonicum* are deposited mainly in the lower bowel.

ology. Penetration of the skin by the cercariae may produce a papular n which may later become vesicular. A similar cutaneous eruption may, er, follow invasion of the skin by cercariae of schistosomes not otherwise enic to man. During the migration of the immature schistosomes transitory may be produced, including areas of pneumonitis. At this stage there is a considerable or great increase of eosinophils in the blood but the alls progressively after the disease is established. In a heavy schistosomal n ova may be found widely distributed in many tissues of the body, ng the central nervous system, liver, lungs, heart and even the skin, but ecies has a special territory for maximum egg deposition. After the s escaped from the vein, a granuloma forms around it. This consists elioid cells, fibroblasts and giant cells surrounded by a zone of plasma cells and eosinophils. When the egg is near a mucosal surface, aide cytolytic enzyme excreted by the miracidium, it may be discharged bowel or bladder. If, however, the ovum is retained in the tissues the mi soon dies and the egg then either disintegrates or becomes calcified, an tissue forms at the site. The degree of fibrosis depends on the intensi infection and the length of time the patient has been exposed to re-i In endemic areas immune processes may limit re-infections.

Clinical Features. The first indication of infection, especially when it i may be tingling and itching of the part which has been exposed to wa taining cercariae. This may last for one or two days and be succeeded symptom-free period of three to five weeks, by allergic manifestations urticaria and eosinophilia and by fever, aches in the muscles, abdomin splenomegaly, headaches, cough and sweating. Patches of pneumor solidation may be present. These allergic phenomena (Katayama syı may be severe in infections with *S. mansoni* and *S. japonicum* but with *S. haematobium*. After one or two weeks these features subside two or three months after the infection there may be no further sy until the deposition of eggs causes fresh ones to develop. The sy then depend on the intensity of the infection and the species of the i schistosome.

Schistosoma haematobium

This species of schistosome affects mainly the urinary bladder a genitalia. The egg is easily recognised by its terminal spine. Man is t natural host.

Geographical Distribution. *S. haematobium* is highly endemic in Eg east coast of Africa and the adjacent islands and occurs throughout Africa, in Iran, Iraq, Syria, Yemen, South Arabia, Lebanon and Israel. occurs in Turkey, Cyprus and in solitary foci in Portugal and the Maha State of India.

Pathology. The urinary bladder and ureters are characteristically af The earliest changes in the mucosa are hyperaemia and petechiae, fo by small granulomata enlarging to form small papillomata but large gr mata may develop in young people. Sloughing may leave an ulcerated s with associated fibrosis. Calcification of dead ova produces, in intense infe 'sandy patches' especially towards the base of the bladder and arou ureteric openings. The lower third of the ureter, including its entrance ir bladder, is liable to stenosis causing partial obstruction to the passage of In severe prolonged infections the bladder wall becomes extensively fi and ultimately may calcify. The capacity of the bladder is greatly dimir The increased intravesical pressure so produced leads to back-pressure kidneys and this alone or combined with ureteric obstruction produces h nephrosis or pyonephrosis and extensive renal damage and uraemia. Ca formation and pyogenic urinary infections may also ensue. Carcinoma

in relatively young males is of common occurrence in some areas of
emicity of *S. haematobium*. Eggs may be deposited in the urethra,
s formation, in the seminal vesicles, vagina, cervix and Fallopian tubes,
along with superadded pyogenic infection may lead to serious pelvic
tions. The rectum may be involved, also the liver (periportal fibrosis),
ess severely than in *S. mansoni* infections. Deposition of ova in the
ry arterioles may lead to hypertrophy of the inner and middle coats
se partial or complete occlusion of some of these vessels. This will
n additional strain on the right side of the heart and lead to cor pul-
These lung changes are especially frequent in combined infections with
atobium and *S. mansoni*. Discrete granulomas in the lung may be large
to be visible radiologically. Ova may also be carried to the central
system, skin and elsewhere.

al Features. The characteristic early localising symptom is usually
l, painless haematuria with or without frequency of micturition. The
uria is usually increased by exercise. When the disease has been estab-
or some considerable time and the bladder has been damaged, all
ms are increased with more haematuria and frequency due largely to
tracted fibrosed or calcified bladder. These symptoms, constant by day
ht, may be very distressing. Pain at this stage is often felt in the iliac
r in the loin, passing down to the groin. In advanced cases pyelonephritis,
ephrosis or pyonephrosis may be accompanied by hypertension or end
mia. Disease of the seminal vesicles may lead to haemospermia. In
fibrosis of the ovaries, occlusion of the Fallopian tubes and vaginitis
icitis may be produced, and schistosomal granulomata may be mistaken
cinoma. Intestinal symptoms may result from lesions in the bowel wall.
severity of *S. haematobium* infection varies greatly, and many with light
ns suffer a minimum of discomfort. However, as the adult worms can
r 20 years or more and progressive lesions develop treatment should be
even when infection is minimal, unless impaired renal function makes
ent dangerous.

Schistosoma mansoni

species of schistosome affects characteristically the large bowel. The
s a lateral spine. Man is the only natural host of importance although
ection is also found in baboons.

graphical Distribution. *S. mansoni* is endemic in the Nile Delta and Libya,
ern Sudan, East Africa continuing as far south as the Transvaal and in
Africa from Senegal and Gambia to Cameroun, throughout Zaire
lso in Arabia. It is also found in South America in Venezuela, Brazil
the West Indian Islands of the lesser Antilles, Puerto Rico and Dominica.

hology. The adult worms reach the tributaries of the inferior mesenteric
nd the female deposits eggs chiefly in the submucosa of the large bowel,

producing early lesions similar to those caused in the bladder by *S.*
tobium—congested spots, granulomata and later papillomata. The pap
in the bowel exceptionally become very large and pedunculated. They
numerous in the lower part of the large bowel but may extend throug
length. Occasionally a segment of the bowel wall becomes infiltra
thickened but remains without stricture or malignant change. In long-
severe infections rectal polypi may prolapse, and secondary pyogenic i
may create faecal fistulae. Eggs may be deposited throughout the body
mesenteric nodes, the small intestine and the subperitoneal tissues. I
infections the liver receives many eggs from the portal vein. This, in comb
with toxic products from the adult schistosomes, may cause periportal
(pipe-stem cirrhosis) with granulomatous changes in the walls of the b
of the portal vein and subsequent periportal formation of vessels and cor
tissue. In the early stage the liver is enlarged, firm, smooth and painl
later it shrinks. The surface shows little or no irregularity. In advance
fibrosis leads to portal hypertension and ascites. The spleen is often
enlarged early in the disease, due to reticulo-endothelial proliferation, b
the development of hepatic fibrosis and portal hypertension the splee
become very large and extremely hard. Pulmonary vascular lesions
marked and lead to cor pulmonale. Eggs may reach the central nervous
and cause a granulomatous space-occupying lesion, the cord being th
usual site.

Clinical Features. The symptoms during the invasion by the cercari
development of the adult worms have been described (p. 62). Depend
the intensity of the infection, symptoms due to deposition of eggs emerg
a period of two months or longer. The characteristic localising sympto
abdominal pain and frequent stools which contain blood-stained mucu
faecal matter is usually solid and its passage over the diseased mucosa
trauma and bleeding. On palpation of the abdomen thickened infiltrated
of the bowel may sometimes be detected. Where the mucosa of the lower
is severely affected, rectal polyps may prolapse during defaecation. H
splenomegaly occurring early in the disease is reversible but in severe
the liver becomes fibrotic and the spleen enlarged and hard, portal hypert
and ascites may develop and the patient dies of haematemesis, hepatic f
or secondary infection. Jaundice is not a frequent feature of this disease.
infection is light no inconvenience may be experienced and the infectio
be discovered only on routine examination of the stool. Other complic
of *S. mansoni* infection include paraplegia from a lesion of the cord a
described under pathology, cor pulmonale. In highly endemic areas the mor
from this disease is considerable.

Schistosoma japonicum

S. japonicum infects particularly the portal drainage of the small int
and upper part of the large bowel. The egg has a lateral knob. The adult
parasitises, in addition to man, the dog, rat, field mouse, water buffal
cat, pig, horse and sheep.

raphical Distribution. *S. japonicum* is prevalent in the Yangste-Kiang China where the infection is a major public health problem. It also ocal distribution in Japan and occurs in the Philippines, Celebes, Laos, d, Vietnam and the Shan States of Burma.

ology. The histopathology of *S. japonicum* lesions is similar to that of ier schistosome diseases in man. As this worm produces more eggs the tend to be more extensive and widespread. The small intestine and part of the large bowel are most affected, and hepatic fibrosis with enlargement is usual. Deposition of eggs in the central nervous system, lly in the brain, causes symptoms of cerebral irritation or compression ut 5 per cent of infections.

ical Features. The clinical features of schistosomiasis due to *S. japonicum* ble those of very severe infection with *S. mansoni*. Dysenteric symptoms e marked, and hepatic and splenic changes are usually early with ascites e development of the superficial abdominal collateral venous circulation. atemesis and melaena may follow rupture of varicose veins in the stomach esophagus. Neurological symptoms include Jacksonian epilepsy, hemi-, blindness and terminal coma. Evidence of compression of the cord may e found.

morbidity and mortality rate in *S. japonicum* infections is greater than either of the other species.

gnosis of Schistosomiasis. A history of residence in an endemic area with toms as described will indicate the need for a careful investigation. An fter contact with fresh water suggests the possible acquisition of this disease, ially if followed, after an interval, by allergic manifestations. In *S. haema-m* infection the terminal spined egg can usually be found by microscopical ination of the last few drops of urine, especially if brisk exercise has been rtaken by the patient before voiding the specimen. The eggs may also be d by microscopic examination of the stool or of a fragment of unstained l mucosa removed through a proctoscope. In a case of some duration a graph may show calcification of the wall of the bladder while intravenous graphy may show stenosis or dilatation of the ureters, reduction in capacity he bladder, or hydronephrosis. Such changes are found commonly in mic areas and have been shown to be frequent even in children, in whom intravesical granulomata are not uncommon. In a heavy infection with *ansoni* or *S. japonicum* the characteristic egg can usually be found in the l. When, however, the infection is light it may be necessary to repeat the ninations over a number of days. Cystoscopy or sigmoidoscopy may enable diagnosis to be made from the macroscopic appearance. Otherwise biopsy imens should be removed and examined for ova. A complement-fixation tion, using an alcoholic extract of fresh livers of *Planorbis boissyi* heavily cted with cercariae of *S. mansoni* as antigen, has proved of value in diagnosis, cially in the early stages of infection. The bowel symptoms of *S. mansoni* *S. japonicum* infection may be very like those associated with intestinal amoebiasis or with a neoplasm of the large bowel, so steps should be to exclude these. There may be concomitant bacillary dysentery.

Treatment of Schistosomiasis. Sodium antimonyl tartrate is probab the most reliable drug for all forms of schistosomiasis. The intravenous must be used, the greatest care being taken not to allow any of the solut leak outside the vein, where it could cause intense tissue reaction and ne Starting with 30 mg the dose is doubled each day, if there are no ill-e up to a maximum of 120 mg. Each dose is diluted in 5 to 10 ml of sterile and the injection is given very slowly as this reduces the chances of toxic e such as cough, vomiting and even acute circulatory failure. If the side- are severe it may be advisable to give the dose on alternate days, dimini daily dose or even discontinue this treatment. The total dosage to cu *mansoni* and *S. japonicum* infection is a minimum of 2 g but for *S. haemat* slightly less may be needed. The drug is given by 18 or more separate injec The patient must rest in bed during the injection and for some hours afterv This is the only really satisfactory course of treatment for the cure of inf with *S. mansoni* and *S. japonicum*.

S. haematobium infections are more easily cured, and various prepar give reasonably satisfactory results. The efficacy of treatment may be ass by the rate of reduction in the number of ova passed, as well as by their abol

An alternative form of trivalent antimony incorporating dimercap stibocaptate. This is administered intramuscularly or by slow intrave injection. The total dose, calculated as 40 to 50 mg/kg body weight, is giv four or five divided doses during a period of four to eight days accordi tolerance. Side-effects, vomiting, general depression and fever may be se especially if the solution has not been made up fresh for each injection.

Niridazole is administered by mouth in a dose of 25 mg/kg body w daily for seven days. Results, especially for *S. haematobium*, are reaso good. Occasionally it produces a temporary psychosis. It is contra-indi if the liver is diseased. The ease of its oral administration and the relat satisfactory results obtained for *S. haematobium* infections have led t widespread use. Dark discolouration of the urine is caused, which shoulc be mistaken for haematuria.

Hycanthone, a new thioxanthone compound, is claimed to produce cu a high percentage of *S. haematobium* and *S. mansoni* infections by a s intramuscular injection of 3 mg/kg body weight (maximum dose 200 m base). The drug sometimes causes vomiting but it is dangerous to admin a phenothiazine (e.g. chlorpromazine).

Surgical aid may be required to deal with residual lesions but large ve granulomata usually respond well to chemotherapy. In cases of chroni *haematobium* infection, ureteric stricture and the small fibrotic urinary blac may require plastic procedures. For rectal papillomata removal by diathe or by other means may give the patient considerable comfort. Granuloma masses in the brain or spinal cord may call for neuro-surgery if the manifestati do not yield to chemotherapy. For portal hypertension splenectomy or a po caval shunt operation may be necessary.

Preventive measures present great difficulties, and so far no really satisfact of controlling schistosomiasis has been discovered. If the ova of the osome in the urine or faeces are not allowed to contaminate fresh water ning the required snail host, then the miracidia will soon cease to be ve.

primitive country bore-hole latrines can easily be constructed but the difficulty is to persuade the people always to use them. In the case of *onicum*, moreover, there are so many hosts besides man that the proper latrines would be of little avail. Mass treatment of the population helps st *S. haematobium* and *S. mansoni* but this method has so far had little ss against *S. japonicum*. An increase in irrigation carries with it a high risk eading schistosomiasis.

ack on the intermediate host, the snail, presents many difficulties. The important snail hosts of *S. haematobium* are species of the genus *Bulinus* *Planorbarius*. In the case of *S. mansoni*, species of the genus *Biomphalaria*, *alorbis* and *Tropicorbis* are the chief intermediate hosts. If an attempt is to kill these snails by draining away the water in which they live they preserve themselves by burrowing into the mud. In the Far East snails e genus *Oncomelania* are the important intermediate hosts. They are very ant to drying. Many molluscicides have been introduced into streams canals in an attempt to destroy these snail hosts but so far without much ess.

rsonal Protection. Contact with infected water must be avoided. Accidental ersion or contact should be followed by a shower and one dose of intraus sodium antimonyl tartrate. Water free from snails, stored for three , will usually contain no living cercariae, but exceptions to this rule have reported.

CLONORCHIASIS

lonorchiasis results from infection of the bile ducts by the trematode *norchis sinensis*. This is a flat elongated worm about 4 cm long which duces numerous ova 19 × 16 microns in size. Dogs, cats and pigs may be cted in addition to man. The eggs are passed in the faeces. To complete the cycle the eggs must be ingested by a freshwater snail and then the cercariae ch escape from it enter a freshwater fish. If this fish is eaten raw or inciently cooked, man becomes infected.

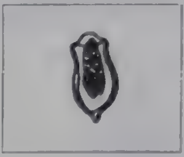


FIG. 6
Clonorchis sinensis.
Ovum (× 250)

eographical Distribution. The infection occurs in China, Korea, Taiwan, an and Vietnam but is more prevalent in South China.

athology. Light infections do little harm. With heavier infections there is a liferation of biliary epithelium and stagnation of bile predisposing to recurrent cholangitis due to *Escherichia coli*. Pseudocysts containing the may form in the bile ducts. The complications are abscesses in the liver a from cholangitis, carcinoma of the biliary duct, and fibrosis of the Cholangitis, associated with the death of numerous worms may present attack of hypoglycaemia. Occasionally the pancreatic duct is dilatec contains many worms, the presence of which predisposes to attacks of pancreatitis.

Clinical Features. In the endemic areas ova are often found in the without symptoms being present. In other cases the presence of the wor associated with epigastric pain of gradual onset or recurrent attacks of pain and jaundice from complicating cholangitis or the symptoms and of the complications detailed above.

Diagnosis. The finding of ova in the stool or fluid aspirated from the duode establishes the presence of the worms but not necessarily the cause o epigastric pain or other symptoms. Ova are sometimes scanty and only i mittently excreted.

Treatment. Treatment in the past has been unsatisfactory but hexach paraxylol 250 mg/kg body weight twice daily on alternate days for 20 is now claimed to be effective but toxic effects have been reported. W secondary suppurative cholangitis ensues, an appropriate antibiotic shoul given and surgical drainage may be required.

Prevention. Fish should be properly cooked before being eaten by ma fed to dogs, cats or pigs.

PARAGONIMIASIS

(ENDEMIC HAEMOPTYSIS)

This disease is caused by a small trematode. There are several specie *Paragonimus* which may affect man, the commonest being *P. westermani*. adult worms live in small cysts in the lung and elsewhere. If a pulmonary

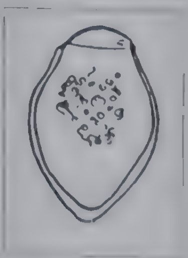


FIG. 7
Paragonimus westermani.
Ovum (× 250)

ruptures, the sputum of the patient contains ova, some of which may be exp torated and the others swallowed and passed in the faeces. From these e the larval worms emerge in water and seek the first intermediate host, a fre water snail. Larvae emerging from the snail enter freshwater crabs or crayfi If man or certain other mammals eat these crustacea raw or inadequately cook infection takes place.

raphical Distribution. Human infections are most frequent in the Far t there are also endemic foci in South America, the Cameroun Republic, a and India.

ology. The adults lie in cysts up to 1 cm in diameter, containing reddish fluid, situated chiefly in the lung. There are seldom more than 20 such resent. In heavy infections cysts may also be present in the pleural or eal cavities, in the brain, muscles, skin or elsewhere.

ical Features. The first symptoms are usually those of slight fever, cough e expectoration of sputum streaked with blood. Occasionally there are of frank haemoptysis with severe pain in the chest. Increasing signs in est may simulate pneumonitis or pulmonary tuberculosis and the latter ntly is a co-existent infection. When the parasites lodge in the abdomen may be symptoms of enteritis or hepatitis. If they settle in the abdominal ey may produce sinuses with a discharge through the skin. Development central nervous system may cause signs of cerebral irritation, encephalitis elitis. The disease may be very chronic and the adult worms may survive years.

gnosis. Ova may be found on microscopic examination of the faeces, m, or a discharge. The radiological appearances of affected lungs are ble but the lesions are usually situated close to the pleural surfaces. Extra-onary lesions are diagnosed in life by biopsy.

atment. Antibiotics are useful to combat secondary pyogenic infections. pecific drug is bithionol (2,2′ thiobis (4,6 dichlorophenol)) given in a dose mg/kg body weight daily in three divided doses on alternate days. In all, 15 days of treatment are required and the results are encouraging. Lesions ised to or maximal in one lobe of a lung may be treated surgically.

evention. In an endemic area crab or crayfish should not be eaten unless uately cooked. Immersion of infected crustaceans in wine or brine does kill the parasites.

FASCIOLIASIS

sciola hepatica, the liver fluke of sheep, occasionally infects man. It is of ric interest that its presence in sheep was described by Jehan de Brie in

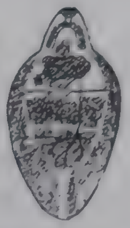


Fig. 8
F. hepatica.
Adult

. The adult worms, which live in the bile ducts, resemble small leaves oximately 3 cm in length. Ova are passed in the sheep's droppings. In water the miracidium escapes from the ovum and enters a snail of the *Lymnaea*, from which cercariae emerge to encyst, as metacercariae, on cress or other aquatic plants, the consumption of which leads to infectio metacercariae penetrate the intestinal wall, peritoneal cavity and liver to in the biliary passages.

Geographical Distribution. The infection in sheep is cosmopolitan. H infections are relatively common in North Africa and occasionally oc Britain, especially in Hampshire, after unusually wet summers.

Pathology. The penetration of the liver by immature worms is asso with toxaemia and causes inflammatory changes and areas of necrosi fibrosis. Numerous adult worms in the bile ducts lead to cystic dilation ducts and the formation of adenomata. Secondary to these changes, and added cholangitis, portal fibrosis may ensue. Inflammatory reactions also around ectopic worms.

Clinical Features. Symptoms and signs may be only those of an ob low-grade fever associated with a tender enlarged liver and an eosinop In heavier infections biliary colic, diarrhoea and signs of toxaemia may c Ectopic flukes may give rise to a nodule in the skin or signs of a lesion i brain or elsewhere.

Diagnosis. Ova may be found on examination of the faeces or duo aspirate but repeated examinations may be necessary. An eosinophilia is expected. A complement-fixation test is of some value but there is a reaction with *Fasciolopsis buski*.

Treatment. A course of chloroquine (150 mg base) twice daily for 14 may relieve the symptoms but injections of emetine hydrochloride, 60 daily for six days, are more effective in overcoming the infection. Bithi (p. 69) has also been used successfully.

Prevention. In endemic areas, watercress should not be eaten.

FASCIOLOPSIASIS

Fasciolopsis buski is the largest trematode to infect man. It was first fo in a sailor from the Far East by Busk in 1843 in London. It is ovoid, 2 to cm × 1 to 2 cm and of a reddish colour. The adults inhabit the small intes of man, of pigs and occasionally of dogs. Ova are passed in the faeces water the miracidia escape and invade a suitable snail, e.g. species of *Segmen* from which cercariae emerge and give rise to metacercariae which encyst edible water plants such as water caltrop or water chestnut. Infection is ticularly liable to occur when man uses his teeth to peel the parasitised pla

Geographical Distribution. The infection is common in Central and So China and amongst Chinese in South-East Asia.

ology. Localised inflammatory changes occur in the mucosa of the upper the small intestine. A moderate degree of eosinophilia is common.

ical Features. Light infections are usually symptomless. In heavier infecirst there is epigastric pain resembling a peptic ulcer, later loose motions ning undigested food are passed. In very heavy infections, particularly dren, generalised oedema may develop and death ensue.

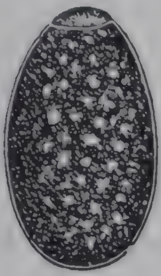


Fig. 9
F. buski.
Ovum (×250)

gnosis. Ova and occasionally adults are detected in the faeces. A lement-fixation test gives also a cross reaction with *Fasciola hepatica.*

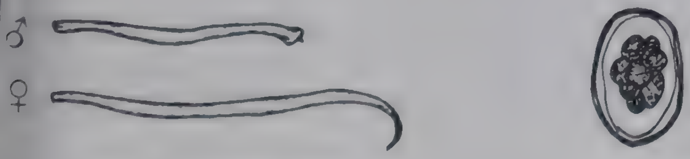
eatment. The usual treatment is tetrachloroethylene as prescribed for hookns (p. 73).

evention. The use of fresh human excreta on the fields is responsible for of the spread of this infection. Prolonged storage of faeces or their treatwith quicklime, destroys the ova or immature worms. Edible water plants be freed of metacercariae by immersing them in boiling water.

ANCYLOSTOMIASIS

(Hookworm Infection)

ncylostomiasis is caused by parasitisation of the small intestine with *Ancyma duodenale* or *Necator americanus.* The adult hookworm is a greyishe nematode about 1 cm in length, approximately the size of a threadworm.



Adults (×2)　Ovum (×250)

Fig. 10
Ancylostoma duodenale.

egg is thin-shelled and oval, slightly smaller than that of *Ascaris lumbricoides* when passed in the faeces two to eight lobes may be seen in the yolk. In m moist soil the larvae develop and reach the filariform infective stage. On ing in contact with human skin they penetrate it and are carried to the lungs. er entering the alveoli they ascend the bronchi, are swallowed and develop e small intestine, reaching maturity in four to seven weeks after infection.

The larvae may also enter through the mucous membrane of the mouth
is the only host.

Geographical Distribution. Hookworm infection is widespread under insa
conditions in the tropics and subtropics and occurs in certain mines in E
A. duodenale is endemic in the Far East and Mediterranean coastal r
and is also present elsewhere in Africa. *N. americanus* is endemic in
East and Central Africa and Central and South America as well as
Far East.

Pathology. At the site of entry the larvae may cause a minor inflamm
and allergic reaction while bacterial infection may raise pustules. When inf
is heavy, reaction to the passage through the lungs may cause a patchy in
mation with areas of pulmonary consolidation accompanied by eosinop
In the small intestine the worms attach themselves to the mucosa by
buccal capsule and withdraw blood. The mean daily loss of blood fron
A. duodenale is 0·15 ml but for *N. americanus* only 0·03 ml. The degree o
deficiency which develops depends not only on the load of worms but al
the nutrition of the patient and especially on his stores of iron. In those
adequate diet regeneration of red blood cells may keep pace with blooc
so that no anaemia may result (p. 124). In the early stage of infection a
siderable eosinophilia commonly occurs.

Clinical Features. In a well nourished person there may be no sympt
the infection being discovered only during a routine examination of the s
At the time of infection hookworm dermatitis (ground itch) may be experie
usually on the feet but it may be on any part of the body which has be
contact with infected soil. An itchy erythema appears first and soon dev
through papules and vesicles to the pustular stage. In a heavy infection
passage of the larvae through the lungs may cause a cough with blood-sta
sputum, associated with patchy pulmonary consolidation (an exampl
Löffler's syndrome). When the worms have reached the small intestine, vom
and epigastric pain, like that of a duodenal ulcer, may ensue. Somet
frequent loose stools are passed, the condition then resembling early spru
giardiasis. In the undernourished, especially when there is a heavy infect
a severe iron deficiency anaemia may develop. This is particularly the cas
children in whom the appearance may simulate the nephrotic syndrome
kwashiorkor, there being often a puffy face, oedema of the extremities ar
distended abdomen, sometimes with ascites. Tachycardia and breathless
are present in those with severe anaemia. In children mental and phy
development may be retarded. Infection with *A. duodenale* usually ca
severe symptoms more readily than does infection with *N. americanus*. C
comitant malaria or other infections aggravate the ill effects of ancylostomi
Untreated heavy infections in the poorly nourished are responsible for m
deaths.

Diagnosis. Iron deficiency anaemia in someone who has been expose
the risk of hookworm infection demands a stool examination to exclude

The characteristic egg can be recognised in the stool either by micro- amination of a smear of the faeces directly or after concentration. ry symptoms similar to those present in the invasive phase of ancylo- may also be produced by the larvae of *Ascaris lumbricoides*, *Schisto-* *Strongyloides* passing through the lungs. The oedema with anaemia differentiated from that due to kwashiorkor, heart failure or nephritis. rms may be present without being the chief agents responsible for ns and signs produced by concomitant associated disease. If hookworms ent in numbers sufficient to cause anaemia, tests of the stool for occult ill be positive and ova will be present in large numbers.

ment. SPECIFIC. The vermicidal effect of most drugs is greatest when er bowel is empty. Accordingly treatment should be given early in the g when the patient has fasted overnight. A well established drug is oroethylene which is given orally. The dose is 0·1 ml/kg body weight maximum of 4 ml. The drug has usually to be given on two or more ns not more frequently than on alternate days. Tetrachloroethylene deteriorates in warm climates and so must be stored in a cool dark

enium hydroxynaphthoate, a quaternary ammonium compound, is an tive drug with few side effects. The dose, irrespective of age, is 5 g, ing 2·5 g base, as a single dose. No preparation or purgation is required. ner dose is necessary for those who continue to pass ova. It is more ive than tetrachloroethylene and is not as effective for *N. americanus* as *duodenale*.

misole in a single dose of 3 tablets each of 40 mg after a light breakfast erately effective against *A. duodenale* and less so against *N. americanus* ay prove to be a further alternative.

-SPECIFIC. The irritation of ground itch can be relieved by the application ointment containing zinc oxide and salicylic acid. Anaemia associated ookworm infection responds well to treatment with iron in adequate (p. **725**). A well balanced diet containing meat and vegetables is desirable. the anaemia is very severe, it should be corrected with iron or blood usion before giving an anthelmintic. In the presence of marked oedema usion is not free from the danger of causing left ventricular failure. Hence d cells rather than whole blood should be employed and the transfusion very slowly. Preliminary digitalisation may be desirable.

vention. Education of the population in the use of latrines should be ged. Bore-hole latrines can be provided in suitable locations near villages. should have concrete plinths so as to avoid contamination of the soil immediate vicinity of the latrine. When the infection is heavy, mass nent of the entire population by tetrachloroethylene or bephenium xynaphthoate is indicated, repeated periodically until the disease has rought under control. The nutrition of the population should be improved. practicable the use of shoes should be encouraged.

STRONGYLOIDIASIS

Strongyloides stercoralis is a very small nematode (2 mm × 40 micron parasitises the mucosa of the upper part of the small intestine in large r The eggs hatch in the bowel and appear in the faeces as rhabditifor which in moist soil moult and become the infective filariform larvae on entering the tissues of man, undergo a development cycle similar of ancylostome larvae. Larvae sometimes mature in the lung. In the a few rhabditiform larvae develop into filariform larvae which m penetrate the mucosa or the perianal skin and lead to auto-infection. the chief natural host, but dogs and cats may also be infected naturally

Geographical Distribution. It is world-wide in the tropics and subtrop is especially prevalent in the Far East.

Pathology. There may be a dermatitis at the time of entry of the larval similar to that which may accompany invasion by ancylostome larvae. intestine the female worm burrows into the mucosa and sets up an inflam reaction; with very heavy infections the mucosa may be severely da leading to malabsorption. Granulomatous changes, necrosis, and eve foration and peritonitis may also occur. An increase in the total wh count with a marked eosinophilia is common in the early stages and th persist. Actively motile larvae are found in the faeces and occasionally sputum.

Clinical Features. An itch may be produced during invasion of the Pulmonary symptoms and signs similar to those of ancylostomiasis ma occur. With slight infections there will be no intestinal symptoms, more severe cases abdominal pain and diarrhoea may be produced, wh on occasions severe; urticaria, anaemia, weakness and emaciation ma be present as well as signs of malabsorption, ileus or volvulus. Penetrat the skin about the anus or the intestinal wall by filariform larvae may le extremely itchy, linear, urticarial skin reactions. These usually subside in hours but tend to keep on recurring. The eruptions may extend 3 or 4 an hour. This rapid progress has led to the term 'larva currens' being rather than 'larva migrans' or creeping eruption. In addition there are frequ urticarial weals or less well defined areas of erythema. These eruptions a to be rare in indigenous peoples. Filariform larvae may reach the brain cause cerebral irritation.

Diagnosis. Intestinal symptoms and characteristic eruptions should su *S. stercoralis* infection. Eosinophilia is usually present. Under the low p of the microscope motile rhabditiform larvae can be seen in the faeces, occa ally in the sputum, urine or bile. Excretion of them is intermittent so rep examinations may be necessary. In ancylostomiasis ova, not larvae, are in a fresh stool. The larva migrans of the dog or cat ancylostome (is located in the superficial layer of the skin and appreciable advance erpiginous dermal lesion takes days, not minutes, as is the case with with strongyloides.

ment. Thiabendazole given orally in a dose of 25 mg/kg body weight ily for two to four days, according to its tolerance, produces a high ge of cures. Some recurrent urticaria may continue for a time and a similar course of thiabendazole may be required.

LARVA MIGRANS

toms may result from various larval nematodes penetrating the tissues in whom development to mature worms cannot take place. Dermal may be caused by the larvae of *Ancylostoma braziliense* or *A. caninum* cat or dog invading human skin, especially the skin of children. The urrows between the corium and stratum granulosum and progresses owly and irregularly, the advancing end showing a skin reaction with while the older part of the burrow is pale and scaly. These larvae may alive and active for several weeks. Treatment by freezing the advancing th ethyl chloride or carbon dioxide snow is not always successful unless ntly repeated. Thiabendazole in a dose of 50 mg/kg body weight for three at intervals of 12 hours or as already described above may succeed.

ction with *Strongyloides stercoralis* may be associated with an eruption ted to its larvae which travels so quickly (p. 74) that the name 'larva s' is appropriate for it.

he Far East (India, Thailand and China) human infection with the third larva of *Gnathostoma spinigerum*, which normally infects dogs and cats, ollow ingestion of raw fish or water containing infected *Cyclops*. Then mmature worm, measuring 6 mm × 0·8 mm usually migrates to the sub- eous tissue where it causes recurrent swellings. The geographical distri- n of this infection distinguishes it from loiasis in which similar 'Calabar' ngs are a feature. The full grown adult worm, which may be as long as may develop in man. When the worm, usually single, is visible through kin it can be removed surgically. During migration in the deeper tissues orm may cause injury to the brain, kidney, lung, eye or other organs. ophilia is usually pronounced. Diagnosis is easy when the adult worm ible. Otherwise complement-fixation tests, using a specific antigen, if ble, will be required. Treatment is not fully satisfactory but some success een obtained with bithionol used as for paragonimiasis (p. 69).

eggs of *Toxocara canis*, the common roundworm of dogs, may be passed faeces and be swallowed by children, causing visceral larva migrans. es are infected prenatally through the placenta, the larvae migrating gh the lung to the upper part of the intestinal tract. There they mature roduce enormous numbers of ova which are excreted in the faeces for six months when the adult worms die. If young children ingest the eggs, ic migration occurs and the larvae may remain alive in the tissues for causing minute granulomatous lesions. This visceral infection in children produce the syndrome of fever, pulmonary infiltration, hepatomegaly, philia, hypergamma-globulinaemia and occasionally encephalopathy. The larvae sometimes reach the eye via the retinal circulation and cause granuloma about the disc or macula, or they may enter the vitreou Blindness of the affected eye may result. There is serological evidence *canis* infection may predispose to epilepsy and paralytic poliomyelitis test, using an antigen from *T. canis*, is available for diagnosis. Rare worms develop in the intestine.

Toxocara cati is regarded as another possible cause of visceral larva in man.

Diethylcarbamazine (p. 79) may give satisfactory results in the treat larva migrans due to *Toxocara*, but preventive measures are all-imp Dogs, especially puppies, should be treated. to remove intestinal worr puppies should not be allowed to defaecate where children are likely to

Eosinophilic lung, as it occurs in the tropics (tropical pulmonary eosin is now commonly attributed to an abnormal host reaction to filarial (p. 84).

FILARIASES

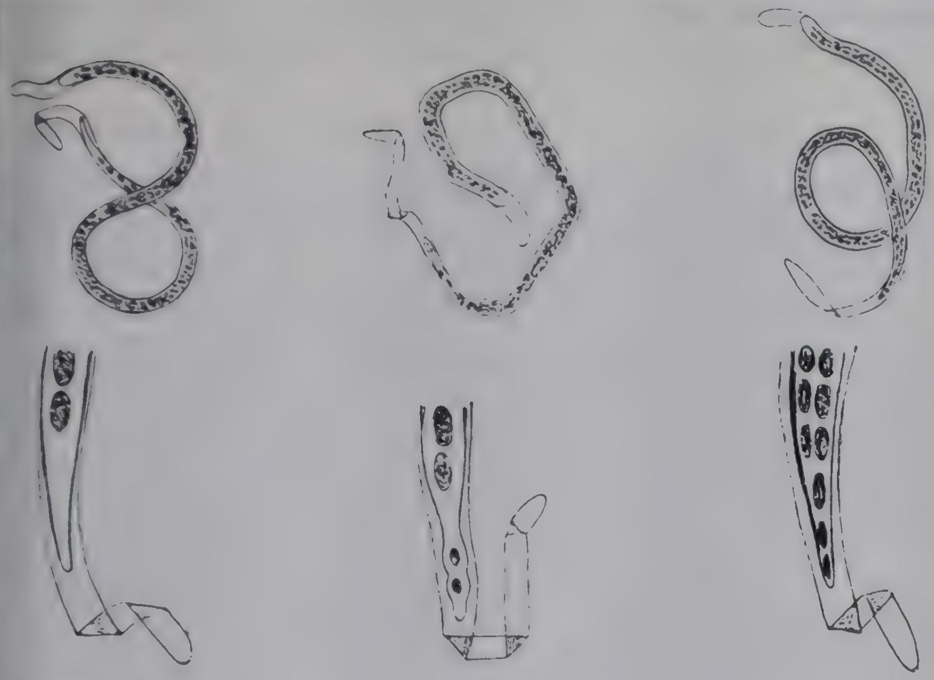
A number of different nematodes of the family *Filariidae* affect ma adults are thin worms varying from 2 to 50 cm in length and the lar microfilariae are easily visible under the low power of the microscope. about 250 microns long. The mature females are viviparous. The adults species *Wuchereria bancrofti* and *Brugia malayi* inhabit and tend to bloc phatic vessels. Adult filariae of the species *Loa loa* wander in the subcut tissue and cause 'Calabar' swellings. The adults of *Onchocerca volvulus* n surrounded by fibrous tissue in subcutaneous nodules but it is their which cause a dermatosis and sometimes serious lesions in the eye. The of *Dipetalonema streptocerca* may produce a similar but milder dermatos *Dipetalonema perstans* and *Mansonella ozzardi*, the larvae of which cir in the blood, are non-pathogenic. The microfilariae have distinguishing mo logical appearances (p. 77). It should be noted that the microfilari *Wuchereria*, *Brugia* and *Loa* are sheathed, the remainder unsheathed.

Wuchereria filariasis

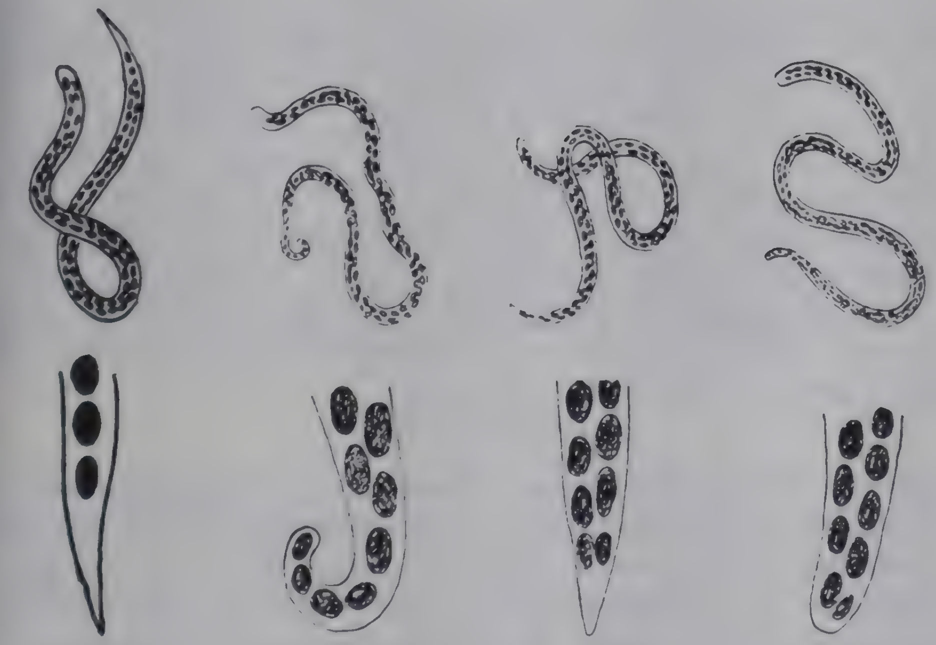
Wuchereria bancrofti is conveyed to man by the bites of infected mosqu of a number of different species, the most common being *Culex fatigans*. adult worms, 4 to 10 cm in length, live in the lymphatics of man, an females produce microfilariae which at night circulate in large numbers in peripheral blood. As *Culex fatigans* bites at night the nocturnal periodici the microfilariae, first demonstrated by Manson in 1877, facilitates the sp of the infection. In some of the Pacific islands there is a non-periodic stra *W. bancrofti* maintained by mosquitoes which bite in the day-time. When circulating in the peripheral blood, the microfilariae are chiefly in the capill in the lungs.

Geographical Distribution. The infection is widespread in tropical Africa. North African coast, coastal areas of Asia, Indonesia and Northern Austr South Pacific Islands, West Indies and also in North and South America.

ogy. The microfilariae do not harm the human host. Light infections ain symptomless but are likely to be associated with an eosinophilia.



W. bancrofti *B. malayi* *Loa loa*



O. volvulus *D. streptocerca* *M. ozzardi* *D. perstans*

Fig. 11
Microfilariae, (×250)
Second and fourth rows show tails (greatly enlarged)

ore intense and repeated infections the presence of mature worms in the atic vessels and nodes lead to granulomatous changes and allergic tissue nses with infiltration of eosinophils around the lymphatics. These cellular changes are associated with attacks of lymphangitis and lead to te lymphatic obstruction. Eventually, after repeated attacks, in some secondary bacterial infections may play a part, permanent obstruct main lymphatic trunk may be produced. Progressive enlargement of or region below the obstruction then follows with thickening and fi the tissues.

Clinical Features. After an incubation period of not less than three the first manifestations are bouts of fever accompanied by pain and te along the course of inflamed lymphatic vessels over which there is cu erythema. In addition there may be some scattered urticaria. Inflan of the spermatic cord (funiculitis), epididymitis and orchitis may be by lymphangitis. After a few days the fever abates and the symptoms a subside. Further attacks are likely to follow and temporary oeden obstructed lymphatics tends to become more persistent, and some enla of regional lymphatic nodes may remain. The lymphatics draining th limbs, the scrotum and the upper limbs are those most frequently a mainly or only in one site in any one individual. The earlier effects may formation of superficial lymph varices, enlargement of lymph nodes production of hydroceles. Permanent obstruction of the main lymphatic of a limb causes progressive enlargement, coarsening, corrugation and fi of the skin and subcutaneous tissue, with warty superficial excrescence a leg resembles that of an elephant. The name 'elephantiasis' is thus to this condition which may also occur in an upper limb, the scrotum or breast. The scrotum may reach an enormous size, a weight of 20 kg o being attained in some who remain ambulant. Obstruction of the abd lymphatics may lead to chyluria or chylous ascites. The interval b infection and the onset of elephantiasis is usually not less than 10 years which the condition tends to be slowly but remorselessly progressive, alt minor degrees may persist unchanged. Gross elephantiasis only de commonly in inhabitants of highly endemic areas where there is no c of mosquitoes. Those who are not well endowed with collateral lymp are especially prone to develop elephantiasis.

Diagnosis. In the earliest stages of lymphangitis the diagnosis is ma clinical grounds, supported usually by an eosinophilia and sometimes positive complement-fixation or intradermal test. After about a year fro time of infection microfilariae appear in the blood at night and can be moving in a wet blood film and identified in stained blood smears. They also be found in the absence of symptoms in some people. They are u present in hydrocele fluid which may on occasion yield an adult filaria. the establishment of permanent elephantiasis it becomes unusual for n filariae to reach the blood stream and eventually the adult worms ma but the lymphatics remain obstructed. Shadows of calcified filariae may s times be demonstrable by radiography. An initial exaggeration of symp following the administration of the specific drug, diethylcarbamazine, is i tive of a filarial infection.

EMENT-FIXATION TEST. This is a group reaction given by all pathogenic The antigen is usually prepared from *Dirofilaria immitis* or *Setaria* riae of animal origin. This test is only positive in a proportion of cases her more reliable, when positive, than an intradermal test using antigens me origin.

nent. Diethylcarbamazine, given orally, has a rapid destructive effect ofilariae and a slower action against adult filariae. The dosage is up 12 mg/kg body weight daily in three divided doses for 21 days. The ge should, however, only be reached slowly, starting with 50 mg (one nd doubling daily if no untoward allergic responses ensue. This course repeated twice at intervals of four to six weeks. To control allergic ena antihistamines or corticosteroids may be required. Treatment with arbamazine, given early in the disease, produces cure and may lead amelioration in the more recently established cases of elephantiasis. tanding elephantiasis a prolonged course of corticosteroids is occasion- eficial. Failing this, plastic surgery, preferably after preliminary radio- investigation of the lymphatics, is indicated. Great relief may be obtained oval of excess tissue but recurrences are probable unless new lymphatic e is established. Tight bandaging, or bed rest with suspension or raising ffected part, by reducing the swelling, will give temporary relief and may rable as a pre-operative measure.

ention. In endemic areas treatment of the whole population with diethyl- azine, 100 mg for adults (50 mg for children) three times daily for days, has reduced infection by robbing the mosquitoes of fresh sources rofilariae. Children are given such a course on starting and just before school. This mass treatment should be combined with control of the by insecticides (p. **970**). Personal protection is obtained by the wearing tective clothing and the use of insect repellents. Where the vector is a biting mosquito wire-screening of the house or the use of mosquito nets t infection. Early chemotherapy prevents later elephantiasis.

Brugia filariasis

gia malayi resembles *W. bancrofti* closely. The microfilaria has distin- ing features and its sheath stains pink more readily with Giemsa's stain the sheath of *W. bancrofti*. The microfilariae usually exhibit nocturnal dicity but a semi-periodic form, which may affect man, commonly infects als. A similar filaria, *Brugia pahangi*, is found chiefly in animals but has transmitted to man. It, or a similar filaria, may be responsible for some of tropical pulmonary eosinophilia (p. 84). The vectors of *B. malayi* are uitoes mostly belonging to the genus *Mansonioides*, the larvae of which air from the underwater stems of water hyacinths or mangroves.

ographical Distribution. *B. malayi* is found in Indonesia, Borneo, Malaysia, am, South China, South India and Sri Lanka.

e pathology, clinical manifestations, treatment and personal prophylaxis are the same as those recorded for *W. bancrofti* except that elephar usually limited to the legs.

Prevention. A selective weed-killer, phenoxylene, has been use success to rid ponds of the water hyacinth and thus to prevent *Mans* from breeding.

Loiasis

Loiasis is caused by infection with the filaria *Loa loa*. The adults, 3 t long, parasitise chiefly the subcutaneous tissue of man. The larval micro circulate harmlessly in the peripheral blood in the day-time, thus show contrast to *W. bancrofti*, a diurnal periodicity. This led Manson in 1 postulate that the vector would be a fly biting by day, such as *Chrysops*, of which are now known to convey the infection. A morphologically parasite infects monkeys but is not readily conveyed to man.

Geographical Distribution. Loiasis may be acquired in West Africa, So Sudan, Zaire and Angola. It is endemic only in and around equatoria forests.

Pathology. The adult worms move about in the subcutaneous tissu other interstitial planes. Usually there is little evidence, apart from an e philia, of a reaction of the host's tissues but from time to time a shor oedematous swelling (a 'Calabar' swelling) is produced, presumably arou adult worm. Calcification of a dead worm is occasionally evident. Encep has been attributed to microfilariae of *Loa loa* on rare occasions.

Clinical Features. The incubation period is commonly over a year bu be as short as three months. The infection may be symptomless. The firs is often a Calabar swelling. This is felt as a somewhat irritating tense loc swelling which is painful only if it is near a joint. The swelling is generally limb; it measures a few centimetres in diameter but sometimes is more d and extensive. It usually disappears after a few days but may persist for or three weeks. Almost invariably a succession of such swellings appea irregular intervals, often in near-by sites. Sometimes there is some urti and pruritus elsewhere. Occasionally a worm may be distinctly seen wrig under the skin, especially of an eyelid and may cross the eye under the junctiva, taking many minutes to do so, sometimes causing irritation. W an adult worm is moving in retro-orbital tissues severe unilateral head resembling migraine is experienced. Encephalitis due to *Loa loa* is probab rare response to the death of numerous microfilariae particularly at the c of treatment, especially if adult worms are situated in proximity to the eye.

Diagnosis. A reliable history of the crossing of the eye by a worm c characteristic Calabar swellings in one who has resided in an endemic enables a clinical diagnosis to be made. This will usually be supported considerable eosinophilia. The demonstration of microfilariae of *Loa l* od (or the recovery of an adult from the skin or eye) establishes the is. Some infections may be too recent for microfilariae to have reached od and in many they are scanty or intermittent in appearance. To strate them a drop of blood, taken at midday, should be examined as ilm under a coverslip. Microfilariae can be seen actively moving and it possible to detect the sheath. Examination of a stained blood film ns the morphology. When microfilariae are scanty, concentration methods ful. The filarial complement-fixation test (p. 79) is positive in 80 per infections and the intradermal test is usually positive. These are not for loiasis (p. 79).

tment. Diethylcarbamazine (p. 79) gradually increased to a dose of 9 to kg body weight daily and continued at that dosage for 21 days is curative t cases. Before diethylcarbamazine was available the removal of a worm ng the eye or moving under the skin was practised but as other adult are almost invariably present this can no longer be recommended. n in treatment is particularly required if there is concomitant oncho- sis (see below).

vention. For prevention a knowledge of the habits of the fly is important. y is attracted by a well-lit room, by movements of persons and also by smoke in native huts. Clearings in the forest of 100 to 200 yards act as a r to *C. silacea*. The most favoured breeding places are the mud flats ed with decaying vegetation bordering slow-running streams. Here the and pupae live for many months. Protection is, therefore, afforded by ing houses sited away from trees and by having dwellings wire-screened st the fly. Protective clothing and repellents are also useful. Mud flats *Chrysops* is breeding should be treated with Dieldrin or other chemicals stroy the larvae and pupae. Treatment of the population with diethyl- amazine will diminish the infective rate of the potential vector.

Onchocerciasis

nchocerciasis is the result of infection by the filaria *Onchocerca volvulus*. adult female may be as long as 50 cm, the male being much shorter. The ction is conveyed by flies of the genus *Simulium* which inflict a painful bite. Vest Africa the vector is *S. damnosum*, in Northern Nigeria also *S. bovis* in East Africa and Zaire *S. neavei*. The flies breed in rapidly flowing well ted water, the larvae being attached to submerged vegetation and rocks. Zaire and East Africa the larval flies may be attached to crabs and fly nymphs. Adult flies bite during the day-time both inside and outside ses. Man is the only known definitive host.

eographical Distribution. Onchocerciasis occurs in well defined areas ughout tropical Africa, in Southern Arabia and also in South Mexico Guatemala.

Pathology. Infective larvae of *O. volvulus* are introduced into the skin bite of an infected *Simulium*. In two to four months the worms mature. A including at least two intertwined living adult worms of different sexe become surrounded by fibrous tissue and a firm subcutaneous nod 'onchocercoma', results. The death of an adult worm may initiate the fi In these nodules, in the tissues around, and widely distributed in th innumerable microfilariae, discharged by the female *O. volvulus*, move a and may invade the anterior part of the eye. Although such microfilaria be present with little tissue reaction, a severe dermatosis and similar reactions in the eye may develop. Occasionally an onchocercoma be necrotic and rarely *O. volvulus* has been found in a subcutaneous absces

Clinical Features. No evidence of the infection, except for an eosino may be present for periods ranging from 9 to 24 months. The first sig be the accidental discovery of one or more subcutaneous nodules, alt the exploring hand is usually guided to their site by some degree of irritation. Nodules are sometimes soft but more usually firm. They are cutaneous but are sometimes attached to underlying bone or to overlying Common sites are around the pelvis or around joints or the ribs and some on the head. They vary in number and size and are painless. An addi or alternative and more common manifestation is a persistent irritating de tosis, at first localised but gradually spreading and appearing also in mu sites. In unpigmented skins this is seen as an erythematous rough ma papular rash, often with excoriations following irresistible itching. In ch infections the skin becomes inelastic, wrinkled and, in places, depigm (leopard skin). Massive infiltration of the skin of the groin may cause it to down in a fold (hanging groin) and localised lymphatic obstruction may pro an elephantoid condition of the skin of the perineum.

In endemic areas the damage done to the eyes by microfilariae has ea the disease the name 'African River Blindness'. Lesions of the eye are likely to be severe in areas of high endemicity. Early features are photoph and conjunctival injection. The cornea may soon show interpalpebral 's flake' deposits and later there may be ciliary injection, chronic iritis adhesions, cyclitis and cataract. A mass of microfilariae in the anterior cha may obstruct vision. Posterior segment changes of choroidoretinitis and atrophy have been described but it is doubtful if these lesions are due to on cerciasis, nutritional or genetic factors being more likely in most cases.

Diagnosis. The finding of nodules or characteristic lesions of the skin eyes, in a patient from an endemic area, associated with a considerable eos philia, is very suggestive of onchocerciasis. Aggravation of the dermat after treatment with diethylcarbamazine supports the diagnosis. A cer diagnosis may be made by removal of a nodule and the demonstratio adult worms and unsheathed microfilariae within it. A skin shaving, repe if necessary from multiple sites, placed in warm saline or water and exam under the low power of the microscope, may reveal the microfilariae. tend to migrate with gravity to the legs so that skin shavings should be t initially from the loose skin below the lateral aspects of the knees or

inity of a nodule. Microfilariae can also sometimes be seen moving in
erior chamber of the eye examined with a slit-lamp or the +20 D lens
ophthalmoscope or identified in a conjunctival biopsy. A filarial
ement-fixation test is positive in about 50 per cent of infections and the
ermal test in a much higher proportion. These are not specific for oncho-
is (p. 79).

tment. Any nodules detected should be removed. Their removal, com-
with a course of diethylcarbamazine, produces cure in a high percentage
es.

thylcarbamazine (p. 79) rapidly kills the microfilariae and this causes an
c reaction for the first few days of treatment. The itch increases, eye
s are aggravated and there may be accompanying fever with pain in the
. Only a small dose should be given initially, 0·5 mg/kg body weight on
rst day, this being gradually increased as the drug is tolerated until, if
ple, a dose of 12 mg/kg body weight is reached. This dose should be
nued for 17 to 21 days. An antihistamine, such as chlorpheniramine
ate 4 mg twice daily, will alleviate these allergic reactions and cortisone
rops will control the reaction in the eyes. The adult worm is more resistant
ethylcarbamazine and it is usually necessary to give two or more such
es of treatment with it.

repeated courses of diethylcarbamazine have failed to effect cure, the
toxic drug suramin, which is more lethal to the adult worms, should be
oyed, as in the treatment of trypanosomiasis (p. 9). For onchocerciasis
ntervals between intravenous injections of 1 g should be five to seven days
the maximum total dose 6 g. Besides curing the dermatosis a surprising
ovement of vision may result from this treatment due to the removal of
ofilariae which were obstructing vision. If suramin alone fails to cure, a
bination of oral diethylcarbamazine and suramin, given intravenously, may
eed.

revention. Mass treatment of infected people with diethylcarbamazine will
ice the infectivity of the vectors. The fly can be destroyed in its larval
e by the application of Dieldrin to streams or the adult flies can be attacked
spraying this insecticide on vegetation near streams. Dimethylphthalate
lied to skin or clothing will repel simulia for several hours. Protective
hing should be worn round the legs to discourage the fly from biting.

Dipetalonema streptocerca

nly the microfilariae of this parasite have been identified in man. They
been found in the skin of man and chimpanzees. The microfilariae are
eathed and are morphologically distinct from the microfilariae of *O. vol-*
s and *D. perstans*. The intermediate host is *Culicoides grahami*.

eographical Distribution. Ghana and Zaire.

Clinical Features. The microfilariae may produce a mild dermatosis trunk, usually less irritating than the dermatosis of onchocerciasis.

Diagnosis. The characteristic microfilariae may be found in skin sh (p. 82).

Treatment. A course of diethylcarbamazine as described for onchoce is effective (p. 83).

Dipetalonema perstans

Dipetalonema (*Acanthocheilonema*) *perstans* is a filarial parasite of man is usually non-pathogenic. In endemic areas microfilariae of *D. perstai* commonly found in the peripheral blood. The adults inhabit chiefly the peritoneal and perirenal tissues and have been found in the pericardia The microfilariae are unsheathed and do not exhibit any periodicity. intermediate hosts are the small flies *Culicoides austeni* and *C. grahami.*

Geographical Distribution. This filaria is found throughout equatorial A as far south as Zambia, also in Trinidad and parts of Northern and Ea South America.

Clinical Features. Sometimes it appears to be responsible for a persi eosinophilia and perhaps occasional allergic manifestations. It has been pected of causing effusions into serous cavities or a cardiomyopathy on occasions.

Treatment. *D. perstans* is relatively resistant to diethylcarbamazine and infection may persist for many years.

Mansonella ozzardi

This filaria of man is non-pathogenic. The adults inhabit the mesentery subperitoneal tissues. The microfilariae, which are unsheathed, circulate in blood. The intermediate hosts are species of *Culicoides.*

Geographical Distribution. West Indies, Central and Northern parts of So America.

Clinical Features. None.

Treatment. None required. Diethylcarbamazine is ineffective.

Tropical Pulmonary Eosinophilia

Tropical pulmonary eosinophilia is a disease of uncertain aetiology. The are indications, however, that it may be caused by an infection with a filar worm such as *Dirofilaria* or *Brugia pahangi*, which is unable to mature in ma ively it may be an unusual host reaction to *Wuchereria bancrofti* or *nalayi*. Microfilariae have been demonstrated by liver and lung biopsy, filarial complement-fixation test (p. 79) has been found to be positive reatment and negative after a course of diethylcarbamazine.

raphical Distribution. The disease is found in many tropical regions ng India, Sri Lanka, Malaysia, tropical Africa, China, Philippines, ia and South America.

ology. Examination of lung tissue has revealed the presence of micro- surrounded by an eosinophilic cellular reaction and giant cells. Blood nation shows a leucocytosis, due to a great increase in the eosinophils.

ical Features. The illness commonly starts insidiously with cough, usually nal and paroxysmal, accompanied by pains in the chest. Sputum is scanty but may be blood-stained. The cough often causes insomnia nay induce vomiting. There may be intervals of freedom from cough ed by recurrence of symptoms, often of increased severity with a rise nperature. The patient's general health deteriorates and weakness and loss ight may be marked. The most characteristic physical signs in the lungs onchi and fine, medium or coarse crepitations. The expiration is usually nged but there is less bronchial spasm than in asthma. Sometimes, how- no abnormal physical signs are found in the lungs and in these cases the complaints may be tiredness and loss of weight. The most common graphic finding is an increase in the normal lung striations, but miliary ing is frequent; enlargement of the hilar glands is also common. Occasion- no abnormality is found in the lung on radiological examination. The ophil leucocyte count is always markedly increased. The erythrocyte nentation rate is raised up to 20 to 60 mm in the first hour. Untreated isease runs a prolonged non-fatal course with periods of remissions and rbations.

agnosis. The diagnosis is suggested by the symptoms and the associated d leucocyte count of not less than 10,000/mm^3, of which at least 20 per are eosinophils. Radiological examination of the chest may help, as also a filarial complement-fixation test. In a patient suspected of suffering from disease the rapid response to specific therapy supports the diagnosis. Pul- ary tuberculosis can be excluded by negative sputum tests and by the onse to treatment. Other causes of eosinophilia such as bronchial asthma, ler's syndrome (p. 72) due to the migrating larvae of *Ascaris lumbricoides* the early stages of other helminthic infections such as schistosomiasis, eosinophilic leukaemia have to be differentiated.

eatment. Excellent results have been obtained with a short course of nylcarbamazine. A dosage of 12 mg/kg body weight daily in three divided s for five days is usually adequate. With this treatment there is a rapid in the eosinophil count, the pulmonary features disappear and the patient's general health improves rapidly. A few relapse and require a further course of treatment.

DRACONTIASIS

(Guinea Worm Infection)

The female of the *Dracunculus medinensis* is a long thin nematode mea a metre or more in length. It inhabits the interstitial and subcutaneous of man and may produce an aseptic synovitis by penetrating a joint. Th is only 2·5 cm long and dies early. The female lives from 12 to 18 m The larvae are passed when the head of the gravid female breaks throu skin. After reaching water the larvae are taken up by a crustacean, C (water flea), in which they develop and become infective in about 21 The infected cyclops is found especially at the bottom of wells and When the cyclops is ingested by man the mature larvae penetrate the int wall and migrate through the connective tissue of the host. After 9 to 18 m the fully mature female seeks the surface of the skin where a vesicle is soon ruptures and exposes the anterior end of the worm. The distended then ruptures and discharges its larvae externally. The worm is attract the surface by cooling, hence the larvae are likely to be expelled into and to be ingested by a cyclops. Man is the most important host but *D. medi* has been found in dogs and cats.

Geographical Distribution. West, Central and East Africa, the Sudan, A Iran, Turkey, Pakistan, Central India, Burma, the Caribbean Islands an northern parts of South America.

Clinical Features. When mature the adult may sometimes be felt beneat skin. Some hours before the head of the worm emerges from the skin is usually some local redness and tenderness. There may also be general all symptoms, erythema, giant urticaria, nausea, vomiting and diarrhoea. T symptoms usually subside as soon as the vesicle has ruptured and the la begin to be discharged. This is usually complete in three to four weeks, which the worm is spontaneously extruded and healing takes place. The ve usually appears in the lower part of the leg or in any area which has kept moist and relatively cool. If the worm dies or is broken during extrac there may be a marked reaction and bacterial infection may occur if pyog organisms are carried into the deep tissue by the retraction of the bro worm. Severe cellulitis, septicaemia, aseptic or pyogenic arthritis followe contractions may result. Tetanus also is a well recognised complication.

Diagnosis. This is usually easy from the appearance of a vesicle and recognition of the discharged larvae. A radiograph occasionally shows calc worms.

Treatment. Diethylcarbamazine may destroy the immature female and h should be used if infection is feared. Allergic features can be counteracte ne and antihistamine drugs. Niridazole (p. 66) is now successfully ed; the dose is 25 mg/kg body weight daily in two divided doses for 10 xtraction of the worm, by winding it gently on a sterile orange-stick, easier and safer by the drug. Antibiotics and prophylaxis of tetanus ll be required in late cases with abscess formation.

ntion. Water supplies should be protected against access of the larvae. n be done by constructing a wall around the well, water then being by means of a bucket. Cyclops may be destroyed by hyperchlorination, n or boiling of the water.

co-operation of the community should be won by advising them as to sons for these preventive measures.

Diseases due to Fungi (Mycotic Infections)

SUPERFICIAL MYCOSES

THE superficial mycoses affecting the skin are very common and occasiona the nails are affected.

Tinea versicolor (Syn. Pityriasis versicolor) is attributed to *Pityrospor* *orbiculare* which produces fine scales of a yellowish or brown colour on t skin of the chest and abdomen. The sternal and interscapular regions are the most commonly affected. The discoloured areas spread at the periphery give a fern-like appearance. There may be slight itching but the complaint chiefly that of the disfigurement; the paler areas in a pigmented skin supe ficially resemble vitiligo or the hypopigmented lesions of leprosy. The absen of sensory changes and the fading margins distinguish the lesions from tube culoid leprosy and the absence of *Myco. leprae* in skin slits and the demonstr tion of the fungus in potassium hydroxide preparations substantiates t morphological differences from lepromatous leprosy and seborrhoeic derm titis. The lesions respond well to weak solutions of iodine, 20 per cent sodiu thiosulphate or to fungicidal ointments as recommended for dermatophytos (see below) but there is a considerable likelihood of a relapse or re-infection.

Tinea imbricata, characterised by multiple concentric rings, is extremel common in coastal areas of some Pacific islands. It responds to griseofulvi (p. 89).

Dermatophytosis (ringworm infections) may be caused by a variety of fung According to the location of the lesion the condition may be described as tine capitis, corporis, cruris or unguium when it affects the nails. The causativ fungi may belong to the genera *Microsporum*, *Epidermophyton* or *Trichophyton* On the body annular or serpiginous lesions with slight itching and no signs o leprosy usually create a characteristic picture, while between the toes the peeling sodden skin, sometimes associated with an unpleasant smell and inflamed surrounding tissues, is well known to doctors and to the lay public under the name of 'athlete's foot'. Infections of the nails are very persistent and cause them to be thickened, distorted and easily broken.

Sometimes in association with dermatophytosis of the feet there is an associated allergic erythematous dermatosis of the palms.

The diagnosis is confirmed by examining under the microscope small scales obtained by scraping the edge of the lesion. These are placed under a coverslip in warm 15 per cent potassium hydroxide solution. The species is determined by culture on special media.

Whitfield's ointment containing salicylic acid and benzoic acid in equal parts in a base of soft paraffin and coconut oil is a long-established remedy and ointments containing undecylenate are also widely used. The fungicide now recommended is tolnaftate, 1 per cent (Tinaderm). If there is much inflammation around the toes, the feet should be immersed in a solution of 1 : 10,000 potassium permanganate twice daily for several days until the reaction has ed. Griseofulvin given without topical fungicides does not eradicate the rom the interdigital clefts but other resistant lesions, including infected nails, respond well to prolonged treatment with oral griseofulvin 250 mg imes daily, although complete eradication especially from toe nails may ears to achieve. In the tropics, because of free perspiration, socks should quently washed and changed.

ea capitis in the tropics does not differ from that occurring in temperate es. It is best treated by oral griseofulvin for three to five weeks.

us. Infection of the scalp by *Trichophyton schoenleinii* produces a mass amy white material with an offensive odour, the lesion being known as or aptly in South Africa as 'witkop' (white head). It is treated by epilation owerful topical fungicides. When social conditions make prolonged oral py practicable griseofulvin has proved remarkably successful.

HISTOPLASMOSIS

stoplasmosis is caused by *Histoplasma capsulatum* (*Darling*) which adopts ast-like morphology in its parasitic phase but is a filamentous fungus enous to soil at other times. A variant, *Histoplasma duboisii*, is found rts of tropical Africa (p. 90). The spores of *Histoplasma* remain viable ears in the soil in which the fungus actually grows, and infected dust, inhaled, conveys the disease. Occasionally infection passes through the al or intestinal mucosa or through the skin. The disease attacks dogs, and mice, and the fungus multiplies in soil enriched by the droppings of kens, pigeons and bats. The infection is thus a hazard for explorers of s.

Histoplasma capsulatum

eographical Distribution. Histoplasmosis occurs in all parts of the United es of America, especially in the East Central States, and less commonly atin America from Mexico to Argentina, in Europe, North, South and t Africa, Nigeria, Malaysia, Indonesia and Australia.

athology. The parasite in its yeast phase multiplies like leishmaniae mainly eticulo-endothelial cells but produces areas of necrosis in which the parasites y abound in enormous numbers. From these foci the blood stream may be aded leading to enlargement of the liver, spleen and lymph nodes. Pulmonary oplasmosis may produce pathological changes similar to those of tuberculosis below).

linical Features. Infection is usually carried to the lung in the first place inhalation of dust containing spores. Probably 90 per cent of pulmonary ctions are benign producing no symptoms, but a more severe infection y closely simulate pulmonary tuberculosis, including the production of a nary complex with enlarged satellite lymph nodes, multiple small discrete ons and occasionally cavity formation. Areas of calcification are charac- stic of the more benign forms of this disease. Lesions of the skin or mucosa

may be found on the rare occasions when infection has entered that wa
are common in disseminated histoplasmosis which is characterised by en
ment of the liver, spleen and lymph nodes, irregular pyrexia, anaemi
leucopenia. An interesting feature is the frequency with which the a
glands become enlarged and caseous, producing symptoms of Addison's di
Diseased heart valves, especially the aortic, are rarely invaded. When the m
of the mouth and gastrointestinal tract become infected, the predom
symptoms may be vomiting and diarrhoea. Occasionally the central ne
system is invaded. The severity of the symptoms of histoplasmosis varies
in the majority of cases, a slight fever of short duration, like influenza,
severe and prolonged pyrexial illness which ultimately proves fatal.

Diagnosis. In an area where the disease occurs, histoplasmosis shoul
suspected in every obscure infection in which there are pulmonary sig
where there are enlarged lymph nodes with or without hepatosplenome
Material obtained by biopsy from a lymph node or the lung should be sta
to show the intracellular *H. capsulatum*. It can also be demonstrated by cu
or by animal inoculation. Radiological examination in old standing cases
show calcified lesions in the lungs, spleen or other organs. In the more a
phases of the disease single or multiple soft pulmonary shadows with enla
tracheo-bronchial nodes may be revealed. An intradermal test is carried
with a 1 : 1000 dilution of a standardised histoplasmin antigen. This giv
positive reaction in most patients with either active or healed infections bu
usually negative in the rapidly progressive form of the disease. A complem
fixation test is positive within three weeks of the onset of an acute prim
histoplasmosis infection and increases in titre as the disease progresses. Precip
tests are also employed.

Treatment. Rest and adequate diet are important. Sulphonamides are
limited value but amphotericin B is commonly used. This drug is prima
suppressive and is not free from serious side-effects. As amphotericin B
poorly absorbed from the intestine it has to be given intravenously. The dos
is 0·5 mg/kg body weight, in 500 ml of 5 per cent glucose over a six-hours peri
gradually increasing to a maximum of 1·0 mg/kg body weight. Daily treatme
is necessary at first in seriously ill patients but later, as improvement sets in,
can be decreased to three times a week. If badly tolerated the dosage may ha
to be reduced. Side-effects are malaise, anorexia, nausea, fever and headach
These can be controlled to a considerable extent by the addition of 10 m
prednisolone to the intravenous solution. Renal and hepatic function tes
should be done during the course of treatment. Amphotericin B may have
be continued for up to a month or longer, depending on the clinical respons
Recovery from generalised histoplasmosis is rare but co-trimoxazole has bee
used successfully.

Histoplasma duboisii

This fungus, first isolated in Ghana, is considerably larger than the classica
H. capsulatum.

raphical Distribution. Ghana, Uganda, Nigeria, Senegal, Sudan and

cal Features. This disease differs in several ways from *H. capsulatum*
n. The bones, skin, lymph nodes and liver may be affected but the
re seldom involved. The visceral form with liver and splenic invasion
fatal, while ulcerative skin lesions and bone abscesses follow a more
course.

ological examination may show rounded foci of bone destruction some-
ssociated with abscess formation. Multiple lesions of the ribs are common
bones of the limbs may also be involved.

tment. The disease is treated in the same way as *H. capsulatum* infections.
ary lesion in bone may require only local surgical treatment.

MYCETOMA

(MADURA FOOT)

1842 Gill of Madura in India described the condition which became
n as Madura Foot. In 1860 Carter gave to this swelling, of fungal causa-
the name 'mycetoma'. This clinical condition, which is not confined to
ions of the foot, may be produced by members of two groups of organisms
ied as *Maduromycetoma* and aerobic *Actinomyceteceae*. A feature common
th groups is the formation by the fungus of grains, with characteristic
rs, ranging from 60 microns to 3 mm in diameter. The incidence of
ent species appears to be related to climate, being especially high when
id hot season ends in rains. The term 'mycetoma' is here used in this
cted sense, although some authors have used the term for other granulo-
us lesions caused by fungi. The more common species of fungi causing
toma, as defined above, are:

Species	*Type of Grains*
Maduromycetoma	
Madurella mycetomi	brown or black (big)
Madurella grisea	black or brown (big)
Phialophora jeanselmei	black
Allescheria boydii	white or yellow (big)
Cephalosporium falciforme	white or yellow
Actinomycetecea	
Streptomyces madurae	white, yellow, red (big)
S. somaliensis	white or yellow (big)
S. pelletieri	red (small)
Nocardia caviae	yellow
Nocardia brasiliensis	white, yellow (very small)

e fungus can be identified by the microscopic appearances of the tissue
grains and confirmed by culture.

cardia asteroides closely resembles *N. caviae* but produces nocardiosis, an
tion in which grains are not produced.

Pathology and Clinical Features. The lesions may occur in any part body but as the fungus is usually introduced by a thorn they are most cc in the foot and leg in peasants who walk bare-footed. At the site of implar the mycetoma begins as a painless swelling, well localised in *Madurella my* infections. Unless totally excised at an early stage, or in some species effe treated by chemotherapy, the mycetoma grows and spreads inexorabl eventually penetrates local bones. The histology is that of a chronic gran with a fibrous stroma and cyst-like spaces in which lie the characteristic g The loose cellular tissue is infiltrated with leucocytes, small round cell giant cells. Nodules develop under the epidermis and these rupture rev sinuses through which mucopus containing the coloured grains is discha Some sinuses may heal with scarring while fresh sinuses appear elsewhere. is little pain and usually no fever, but progressive disability. Secondary pyc infection does not usually penetrate far down the sinuses, possibly becau antibiotic activity of the fungi.

Madurella mycetomi grows in fascial planes and avoids the muscles a very late stage; it does not affect nerves and tendons. Although pig may be carried to regional lymph nodes, it is exceptional for the fungi reach the nodes unless there has been surgical interference. When the le is in the scalp, the skull may be affected but the dura mater appears to b effective barrier. Apart from involvement of bones by a spreading mycet intra-osseous lesions may be found in the metaphysis of a long bone, espec at the upper end of the tibia and sometimes there may be an encapsul periosteal mass.

Nocardia brasiliensis often affects the skin of the back. It is seldom loca and may spread widely.

Streptomyces somaliensis and *S. pelletieri* also spread insidiously and e invade muscle. As in the case of *S. madurae* they also readily reach regic lymph nodes.

Extensive damage of bones may be caused in any of these infections.

Treatment. The difference between *Maduromycetoma* and *Actinomycetece* crucial in that there is no drug of proven efficacy for the former. Amphoteri B is apparently inactive *in vivo*, though not necessarily *in vitro*, against b *Maduromycetoma* and aerobic actinomycetes that cause mycetoma. Spora successes with griseofulvin against the *Maduromycetoma* have been report but the results have been mostly disappointing. Experimental work is still goi on with newer products like BAY b 5097 but up to the present maduromycetor requires to be surgically removed. Mycetoma has a strong tendency to rec locally unless the excision has been adequate or the amputation high enoug The treatment of actinomycetoma is more hopeful. Dapsone frequently giv good results with infections due to *Nocardia* species. Sulphonamides also ha some value. It is important to give the drug in an adequate dose for a lor enough time. There are reports of the successful treatment of actinomycetom due to *Streptomyces* species with dapsone, sulphonamides and broad spectrur antibiotics but there have also been many failures. Perhaps the most promisin agent currently available for this group is co-trimoxazole. Nevertheless, it mus be admitted that many cases still require surgical removal.

NOTES ON OTHER MYCOSES

Blastomycoses

American Blastomycosis is caused by *Blastomyces dermatitidis*. It also n Africa. This infection may give rise to cutaneous lesions, especially ce. Systemic infection begins in the lungs and mediastinal lymph nodes mbles pulmonary tuberculosis. Bones, the central nervous system and to-urinary tract may also be affected.

teral treatment with 2-hydroxystilbamidine (p. 4) or slow intravenous s of amphotericin B has achieved much success. Co-trimoxazole may effective (p. 90).

American Blastomycosis (*Paracoccidioidomycosis*) is caused by *Blasto- rasiliensis*. Mucocutaneous lesions occur early. Involvement of lymphatic nd the lungs is prominent and the gastrointestinal tract may also be d.

nged treatment with oral sulphonamides or slow intravenous infusions hotericin B may be curative. 2-hydroxystilbamidine may be successfully ed.

diagnosis and differentiation of blastomycosis is established by culture ungus from the pus expressed from the lesion, or in systemic infections he sputum. Complement-fixation reactions and intradermal tests aid sis.

Chromoblastomycosis

(Mossy Foot)

mossy foot is a fungal infection and is to be distinguished from the excrescences which accompany the chronic lymphatic obstruction of ntiasis and also from Madura Foot or mycetoma. Chromoblastomycosis to certain species of *Cladosporium*.

se fungi are acquired on splinters from decaying timber and give rise to y condition of the foot and also rarely affect the face, upper limbs, vulva ain. The diagnosis is confirmed by the recognition of dark brown spheroid 4 to 8 microns in diameter in biopsy specimens. These fungi grow readily bouraud's medium.

atment. Iodides up to 3 g daily and calciferol 1 to 2 mg weekly should ven. This is combined, when necessary, with surgical removal of local s but relapse is common. Amphotericin B by 'blast' injection is now con- d the best treatment.

Sporotrichosis

rotrichosis is caused by *Sporotrichum schenckii*. The infection occurs ghout the world and is prevalent in Central and Southern Africa. It s swellings resembling gummata or a chancroid type of ulcer and affected lymphatic vessels may be thickened and palpable as a chain of nodul commonly dissemination takes place into lungs, bones, the central system and elsewhere.

Diagnosis. The fungus can be cultured from discharges or biopsy mat

Treatment. Potassium iodide up to 10 g daily should be given orall some time after apparent clinical cure and into the lymph nodes a s containing iodine in the proportions of 1 g iodine, 10 g potassium io 500 ml of water should be injected. Widely disseminated infections are s fully treated only by amphotericin B.

Cryptococcosis

(TORULOSIS)

Cryptococcosis is caused by *Cryptococcus neoformans*. It occurs in California, Central United States and elsewhere and causes local gumm like tumours and granulomatous lesions of the lung, bones, brain and men The cerebrospinal fluid often contains the fungus when the nervous syst affected.

Diagnosis. This is made by serological tests, biopsy or culture.

Treatment. Amphotericin B should be given by slow intravenous inf and, in disease of the nervous system, intrathecally. It has been suggested experimental work that a low thiamine diet and gamma globulin injec may be a useful supplementary measure. Some cases of cryptococcal menir have been cured by oral 5-fluorocytosine, 100 to 200 mg/kg body weight daily until the cerebrospinal fluid remained normal. Surgical removal of pulmonary lesions is essential to prevent spread to the brain. Recovery ma assessed by serological changes.

Coccidioidomycosis

Coccidioidomycosis is caused by *Coccidioides immitis*. This infection is fo in Southern United States, and in Central and South America. The disea acquired by inhalation. In 40 per cent of cases it affects the lungs and ly nodes. Rarely it may be carried by the blood stream to the bones, adre meninges and other organs. Infected sputum dribbling on to the chin prod a characteristic skin lesion. In 60 per cent of cases the infection is asymptom Infections, including subclinical attacks, are followed by immunity.

Diagnosis. The fungi appears as spherules, 11 to 70 micromicrons in diam with a thick hyaline capsule containing numerous endospores. These g readily on culture media but as they are highly infective, diagnostic inve gations are usually limited to intradermal, complement-fixation and precip tests.

ment. Some localised pulmonary lesions can be successfully treated by . The only treatment other than surgery which may be beneficial is the ministration of intravenous infusions of amphotericin B.

Rhinosporidiosis

osporidiosis is caused by *Rhinosporidium seeberi* and occurs in South a, India, Sri Lanka, East Africa and elsewhere. This organism forms a ich on rupture discharges spores which spread by lymphatics to con- tissue. It produces polypi in the nose and localised swellings on the nd elsewhere.

nosis. The characteristic sporangia and spores are recognised on histo- examination of the tumour-like tissue but the organism has not yet ultured.

tment. This consists of excision and intravenous pentavalent antimony Amphotericin B is required for resistant cases.

Miscellaneous Conditions

THE CHIGOE FLEA

INFESTATION with *Tunga penetrans* (the chigoe or jigger flea) is importan number of tropical countries. Originally found in tropical America, i introduced into Africa where it is widespread.

Clinical Features. The female *Tunga penetrans*, when impregnated, bu into the skin of man, especially about the toes and soles, but the fingers and parts of the body may be invaded. The flea then develops enormously, becon large as a pea and is packed with eggs in a cyst-like cavity. Ultimately the eg discharged on to the surface of the body. Man and pig are the principal host cats, dogs, and rats may serve too. Untreated, the site of infestation may be irritated and inflamed but the chief danger is from secondary pyogenic infec The anaerobic tissues around the chigoe are also suitable sites for the dev ment of tetanus.

Treatment. An attempt should be made to remove the chigoe and eg complete but if it is ruptured no harm results if a mild antiseptic ointme applied after removal of the chigoe and eggs. It is essential to avoid the ir duction of bacteria by insisting on the use of a sterile needle when removin chigoe. Massive infestations, such as may be seen in neglected children an senile persons, should be treated by immersing the feet in a bath of an aque solution containing benzene hexachloride powder (BHC) 5 per cent and C mide powder 0·8 per cent.

Prophylaxis. The floor should be kept clean and sprayed with an insectic Shoes should be worn and the feet should be inspected daily, especially aro the nails.

POROCEPHALOSIS

This name is given to invasions of the body by 'tongue worms', degener arthropods of which *Armillifer armillatus*, *A. moniliformis* and *Linguatula serr* occur in man. Adult *Armillifer* parasitise the trachea and bronchi of snakes. M is infected by ingesting ova on uncooked vegetables or by eating snakes. T condition is usually symptomless in man but calcified nymphs may be seen radiographs of the chest and abdomen.

'Halzoun', the name given in the Middle East to acute dysphagia and laryng obstruction, due to pharyngitis and oedema of the larynx, following the eating raw goat's liver was formerly attributed to invasion by immature *Fasci hepatica* worms. It is now believed to be due to the ingestion of nymphs *Linguatula serrata*. These may be obtained by eating the raw liver of goats sheep but more commonly from the accompanying inadequately cooked lym nodes of goats. Foxes and dogs are the definitive hosts and wild rodents or goa rmediate hosts. Less commonly sheep are affected. Antihistamines and a naesthetic spray are suggested for treatment.

MYIASIS

asis is an infestation of various tissues of man by the larvae of flies.

Cutaneous Myiasis

ommon cause of cutaneous myiasis is *Cordylobia anthropophaga* (Tumbu he larva penetrates the skin and produces a lesion like a boil. The eggs which the larvae arise are liable to be laid on laundry spread on grass. ther cause in the tropics is *Dermatobia hominis* which deposits its eggs on ntral surface of the abdomen of other *Diptera*, especially mosquitoes. the mosquito bites man or other animals, the warmth of the body ates the emergence of the larva. It burrows through the mosquito-made l into the subcutaneous tissue and grows, causing a rounded swelling with ral orifice through which it obtains air. After reaching maturity it escapes. ionally the common warble fly (*Hypoderma bovis*) may infest man. *hmeromyia luteola*, the Congo floor maggot, imbibes blood through the dropping off when disturbed.

atment. The treatment of cutaneous myiasis consists of widening the ng in the skin, if necessary, and removing the larva.

Myiasis of Wounds, Sores and Cavities

e larvae of many flies including *Callitrogra hominivorax* (Screw worm), *fahrtia*, *Calliphora*, *Lucilia*, *Sarcophaga* and *Fannia* may infest necrotic in open wounds or ulcers and occasionally invade living tissue. Chronic cal ulcers and necrotic tissue from leprosy or tertiary yaws of the nose and ynx may be invaded. *Chrysomya bezziana* is a myiasis-producing fly which und in Africa, India and South Vietnam. It may penetrate the nasal sinuses cause great tissue destruction. *Wohlfahrtia magnifica* is the only specific sis-producing fly known to infest man in Europe.

eatment. The application of 10 per cent chloroform in a light vegetable oil is reatment of choice for infested wounds.

Intestinal Myiasis

the tropics especially, vague digestive disturbances or abdominal cramps diarrhoea and vomiting may be caused by dipterous larvae in the intestinal . The eggs or larvae are ingested with food, but it is also possible for flies to sit eggs on the skin around the anus whence the larvae may crawl into the m, vagina or even up the urethra and reach the bladder. Species of the a *Fannia* and *Sarcophaga* are most frequently encountered. When larvae are swallowed they are passed in the stool or vomited. All fly larvae found i stool have not necessarily been passed from the bowel as in tropical climates eggs deposited in faecal matter rapidly hatch out into larvae. Occasionally l of *Aphiochaeta* or *Megaselia* may pupate in the bowel and live flies escape the anus with the stool.

Treatment. An aperient is usually all that is required.

Aural Myiasis

When there is an aural discharge, myiasis may be caused by the larva *Callitrogra hominivorax*, *Sarcophaga*, *Calliphora* and *Fannia*. The nasal cav and eyes may also be infested, and serious destruction may result.

Treatment. Instillation of 10 per cent choloroform in a light oil kills larvae.

Ocular Myiasis

The maggot of *Oestrus ovis* sometimes infests the human eye. The egg ma deposited in the eye of someone tending sheep, even without the fly alighting stinging sensation is felt, followed, as the larva develops, by severe pain in eye. A drop of cocaine is required so that the lids can be opened to allow extr tion of the maggot.

POISONOUS BITES

Snake Bite

Poisonous snakes belong to five families.

1. *Colubridae*, many of which are non-poisonous, include the Opisthoglypl which are poisonous but only rarely dangerous to man because the grooved fan are the most posterior teeth in the upper jaw. Examples are tree snakes.

2. *Elapidae* have forward grooved fangs. The fangs are fixed in the upper ja below or in front of the eyes. The nostrils are lateral and there are large scal over the head. The family includes cobras, kraits and mambas.

3. *Hydrophidae* are poisonous sea-snakes; they have an eel-shaped tail an rather flattened body. Sea-snakes are found along the shores of the Indian an Pacific oceans and are mostly poisonous. The most common dangerous species *Enhydrina schistosa*. *Laticauda colubrina*, the banded sea snake or 'coral snake' poisonous but not aggressive.

The *Elapidae* and *Hydrophidae* both belong to the Proteroglypha, so name because the fangs lie anteriorly.

4. *Viperidae* are true vipers, including Russell viper and adders. At rest th long canalised fangs lie along the palate pointing posteriorly but during the act o biting they are rotated forward.

rotalidae include the pit viper (pit between the nose and the eye) and the nake.

Viperidae and *Crotalidae* both belong to the Solenoglypha, the term ting canalised fangs.

ke venom is secreted as a specialised saliva from modified parotid glands. ain function is to immobilise the prey but it appears also to assist in ion. The venom may contain cellular debris and bacteria from the snake's h, e.g. *Cl. welchii*. The active agents in venom are enzymes which are anti- ; hence specific antisera can be prepared.

e amount of venom injected depends on various factors. A bite through ng is less dangerous than one on the naked skin. The interposition of ing makes a considerable difference to the bites of *Elapidae* as the fleshy ing of their grooved fangs is pushed aside and venom is lost on the surface e skin, whereas the fully canalised fangs of the *Viperidae* enable venom to be arged into the depths of the wound. Also the latter's poison glands are ied ('wrung') more efficiently during the process of biting.

thology. The venoms of *Viperidae* and *Crotalidae* usually contain various erful enzymes which are cytolytic and may also be haemolytic, cause haemo- ges or intravascular coagulation. The result is the production of a great ling and necrosis of the tissues at the site of the bite.

e venom of the *Elapidae* is typically a powerful neurotoxic agent with only a t cytolytic action, so producing very little local reaction. There are, however, ortant exceptions to this general statement, e.g. the Indian cobra. It is, efore, prudent to acquire information about local poisonous snakes and the ropriate treatment for each so that the correct therapy may be made avail- .

ydrophidae secrete a potent venom containing a myotoxin which produces osis of muscles.

linical Features. The bites of *Viperidae* and *Crotalidae* are characterised by a found local effect on the tissues at the site of the wound. Severe pain, great lling and discoloration from haemorrhage and oozing of blood-stained um are usually followed by sloughing. General symptoms, when pronounced, those of cardiovascular shock accompanied by nausea and vomiting. If the om has gained access to a vein, the victim may die in a few minutes from sive intravascular clotting. When, more commonly, the venom is injected avenously, the patient may bleed from the lung, or die of cardiac failure ciated with severe anaemia. Local sloughing is often complicated by ndary sepsis and may be followed by gas gangrene or tetanus.

lapine bites may show few local signs apart from some numbness and some y muscular weakness. Within two hours there follows the sequence of oping eyelids, unsteady gait, incoordinate speech and difficulty in respiration. er general and bulbar paralysis develop, with difficulty in swallowing, aphasia cyanosis. The heart is not primarily affected, and consciousness is retained near the end. Death may come within six hours or be delayed for one or days.

Fishermen dragging nets ashore in muddy water, at or near a river mout the usual victims of bites by *Hydrophidae*. Bathers and paddlers are se attacked. The bite on ankle, foot, wrist or hand is felt as a sharp prick but t after is painless, inconspicuous and without local swelling. Systemic pois follows in only a quarter of those bitten. In these, symptoms appear withi hour and consist of pain and stiffness, initially in the muscles of the neck, and proximal parts of the limbs but rapidly becoming generalised. Passive m ments provoke intense pain. Later, in severe poisoning, trismus, ptosis external ophthalmoplegia may appear. Three to six hours after the onse poisoning, the urine contains myoglobin and protein. Death may result f extensive paresis leading to respiratory failure or from renal failure. If poiso is less severe, the victim survives but muscle weakness may persist for mor

Treatment. The following first-aid measures can be carried out by untra personnel. First determine, if possible, whether the bite is of a poisonous sn by examining and retaining the snake, if available, and by searching the bite fang punctures. As most people bitten by a snake suffer from fright and fea death the patient must be reassured that fatal results from snake-bite are common. The patient must be kept at rest and a constricting ligature such a handkerchief applied above the wound sufficiently firmly to retard the flow in veins and lymphatics draining the bitten area but not to stop the arte circulation. The ligature must be released for one minute in every thirty. Ven on the surface of the wound should be wiped away gently with a cloth or wash away with plain water. The bitten part should be immobilised as for a fractu and an analgesic such as aspirin but not morphia may be given. Medical should be obtained as soon as possible.

The further treatment depends on the type of venomous snake.

In Britain *Vipera berus* is the only poisonous snake, and its bite is less dang ous than is the use of antivenom. The only antivenom available is that prepar for use against *Cerastes cornutus*, a South African viper, and its effica against *Vipera berus* is unproved and its use is not recommended. As soon medical care is available, the further treatment of a viper bite in Britain is t injection of 100 mg hydrocortisone intramuscularly, 1 to 2 mega units penicillin and a 'recall' dose of tetanus toxoid or, in the unprotected, 2,000 uni of tetanus antitoxin. The lightly applied tourniquet will subsequently be release with increased frequency.

In countries where a highly venomous land snake may have bitten a perso further treatment as discussed below can be given by non-medically qualifie persons who have had first-aid training. Specific or polyvalent antivenom 10 t 30 ml may be given by the intramuscular route using one or more sites of injec tion. The dose of antivenom must be repeated after four hours. It should b remembered that a child requires as large a dose of antivenom as an adult. At th same time, to lessen the risk of anaphylaxis, 1 ml of adrenaline injection B should be given slowly intramuscularly and half this dose can be repeate 15 minutes later. Prednisolone 30 mg is given by mouth or hydrocortison hemisuccinate 100 mg intramuscularly. Ice bags are applied to the bitten part which, however, must not be immersed in ice or ice-cold water. Penicillin and anti-tetanus treatment are given as well.

n a doctor is available the same treatment is recommended but the anti- should be given in the same dosage by the intravenous route. Except in e urgency it is advisable to give a trial dose of 0·2 ml antivenom intra- larly and to observe the patient for 30 or preferably 60 minutes for signs phylaxis before the therapeutic dose is injected intravenously. The intra- lar route may be used for children with small veins. Incision into the n part is indicated only when there is marked swelling likely to cause ene, and this should be undertaken only by a medical man.

se bitten by sea-snakes should be given similar first-aid treatment, being t rest and transported by stretcher to hospital. If more than one hour s after the bite without the appearance of signs of toxicity only reas- ce is required. If there is clear evidence of systemic poisoning specific anti- should be given intravenously, preferably after testing for anaphylaxis. A of 2 to 3 ampoules is advised but this should be increased to 4 or 5 ampoules ns of severe systemic poisoning are present. Acute renal failure and ular weakness may be treated successfully by renal dialysis.

ERAL MEASURES. Shock should be combated by rest, warmth and fluid by h or intravenously, and blood should be transfused when indicated. To ol haemorrhage calcium salts and vitamin K may be useful. Respiratory ness following an elapine bite will benefit from oxygen and respiratory lysis by mouth-to-mouth breathing or by the intratracheal method. Bacterial tion is more likely in *Viperidae* and *Crotalidae* bites, and here penicillin, us toxoid or antitoxin and anti-gas gangrene serum are especially useful.

Spider Bite

he venom of certain spiders is dangerous to man. One of them is *Latrodectus tans*, the 'black widow' spider. The adult female is glossy-black with crimson r-glass markings on the ventral aspect of the abdomen. In South Africa *ndistinctus*, the 'button' spider, is also poisonous as is *Atrax robustus*, the eral web' spider, in Australia. Many other poisonous arachnids are found in erent parts of the world. With the bite venom is injected and this causes ere local pain followed by redness and swelling. Soon pain is intense, first in adjacent muscles but spreading rapidly to all voluntary muscles, especially flexor groups, causing severe spasms. Contraction of the pupils, salivation sweating are common, and in severe cases the patient may suffer cardio- cular collapse. Rigidity of the abdominal muscles may simulate an acute omen. Later the site of the bite may slough.

reatment. The bite should be cleansed. Local incision and suction may ove some of the venom. Where a specific antivenom is available this should njected into the muscles near the bite. If convalescent serum is available it be tried. A good response may be obtained to an injection of atropine. ticosteroids are of value. For the relief of muscle spasm 10 to 20 ml of 10 per t calcium gluconate can be given slowly intravenously. Antibiotics should be d against secondary pyogenic infections.

Octopus Bite

The octopus seizes its prey by its eight tentacles and inflicts a painfu which is not, however, usually dangerous.

Tick Paralysis

Animals and occasionally man suffer from fatal poisoning due to ve excreted by the salivary glands of certain *Ixodidae* (hard ticks). This is espec likely to follow the attachment of the tick to the head or neck for some day flaccid paralysis may develop followed by failure of respiration. Removal o tick, in time, leads to recovery.

POISONOUS STINGS

Scorpions

There are many genera of scorpions found in the tropics and subtrop Paired poison glands are situated in the terminal segment of the flexible join tail which is curved dorsally over the scorpion's body before striking.

Clinical Features. There is a single puncture wound at the site of the sti Intense local pain is felt immediately, and a red oedematous weal, sometir haemorrhagic, soon appears. Children particularly show severe general syn toms which include sweating, salivation, nausea, vomiting and depression respiration and may die. From S. India and Jordan occasional deaths of adu also are reported and recent observations point to disseminated intravascu coagulation resulting in defibrination and haemorrhages as the cause of dea In Trinidad stings of the scorpion *Tityus trinitatis* frequently cause acu pancreatitis from which recovery is usual.

Treatment. Pain can be relieved by applications of ice-cold water or by t local injection of xylocaine and adrenaline. When a young child has been stun the site of the sting should be cleansed with soap and water and incised. Loc suction is then of value in removing some of the venom. If antivenom is availab the child should be given 5 ml of the serum intramuscularly near the sting as ear as possible. When required, general treatment for shock is given. The value corticosteroids is under investigation and in severe cases continuous intraveno heparin would combat disseminated intravascular coagulation.

Bee Stings

A bee sting is always painful and in those who have become sensitised a anaphylactic reaction may result in rapid death. In the majority of fatal case there has been a severe reaction to a bee sting on an earlier occasion. Desensitisa tion may be practised with some degree of success. Emergency treatment o anaphylactic shock consists of 0·5 ml of adrenaline injection BP given intra muscularly followed by an intravenous injection of hydrocortisone hemisuccinat

g. Anyone who has sustained a severe reaction should, however, be ed with the means of self-administering a subcutaneous injection of 0·5 ml naline injection BP in an emergency and should also carry a drug such as naline, 10 mg of which placed under the tongue produces rapid stimulation ympathetic nervous system. Less severe symptoms may be relieved by an tamine. Multiple stings are more dangerous than single stings and the rs' of the bees should be removed from the skin as they continue to release until this has been done.

Jellyfish

ious jellyfishes cause lesions in the skin and general reactions in man. ng by the Portuguese man-of-war, *Physalia*, is commonly associated with reactions. The long filamentous tentacles hanging from its under surface n poison glands which release a toxin when they come in contact with the n skin. Linear reddish-brown weals are produced in the affected areas of Excruciating local pain is felt, and soon general symptoms may follow, ling profuse sweating and severe griping abdominal pains. Very occasionally ent dies within a short time of being stung by a jellyfish, in which case one *Cubomedusae* (sea-wasps or box-jellies), *Chironex fleckeri* or *Chiropsalmus* *igatus* is probably responsible. Their tentacles contain numerous charac- c stinging organs which have been identified in the lesions of those who have mbed. The stings are very painful. At postmortem the lungs and air ges have been filled with frothy mucus and the abdominal organs and brain ongested. 'Irukandji stings' affect bathers in the sea off N.E. Australia at n seasons. They are caused by minute Carybdeid (simple sea-wasps). Acute ning develops in a few minutes characterised by violent abdominal and alised pains, vomiting and prostration. The victim appears seriously ill for a lays but always recovers.

eatment. The exact nature of the poison is not known but in severe cases the muscular injection of an antihistamine drug should be employed without y. Corticosteroids may also be of value. The stinging organs may adhere to phane tape applied over the affected area and be withdrawn when this is oved. A cream or ointment should not be applied as this spreads the affection.

Cone Shells (Conidae)

ere are many varieties of cone shells. The occupant is often poisonous and give a sting causing death by respiratory paralysis.

Stinging Fish

e stonefish (*Synanceja trachynis*) is the most deadly of the stinging fish and n easily be mistaken for a piece of coral. Along its back are 13 large spines containing paired poison sacks. The poison causes great pain and swelling e sites of the stings and may cause death from respiratory paralysis. Hot r destroys the poison and an antivenom is available.

The stingrays (*Dasyatidae*) are flat fish lying on the sand or mud. disturbed a painful sting may be inflicted from a poisonous spine of the

Poisonous Fish

There are a number of fish which may be poisonous to eat. Examples a pufferfish (*Tetraodontidae*), porcupine fish (*Diodontidae*) and boxfish (*ciontidae*). In general, fish covered with hard plates or spines may be poiso and the skin and liver, in particular, are dangerous to eat.

TROPICAL PHLEBITIS

This phlebitis, of uncertain origin, was first described in East Africa but is known to occur throughout tropical Africa.

Pathology. Vascular granulation tissue containing fibroblasts, endothelial and giant cells is laid down, especially in the middle coat of the vein but ext outside the wall of the vein. Thrombosis takes place in the vicinity of the le and distal to it. Thrombosis of the splenic vein may cause necrotic infarction liquefaction in the spleen.

Clinical Features. The effect of these changes in a vein depends on its When the vein is large, there will be a marked reaction in it with pain alon course, followed by local swelling and enlargement of the veins and tissues d to the lesion. It may be possible to palpate the affected vein as a hard cord- structure. There is usually a febrile reaction during the acute stage. The ven lesion gradually resolves and the circulation is re-established. When the dise veins are small, the symptoms and signs are slighter. Painful thickenings of or several superficial veins may be palpated. These usually resolve in a few we

Diagnosis. This is made by a history of local pain over a vein, with swelling constitutional disturbance. When one of the larger veins is affected, the ini symptoms may resemble those of tropical myositis. Meningitis may be simula by phlebitis of veins in the neck.

Treatment. This is symptomatic. The value of treatment with anticoagula has not been determined.

TROPICAL MYOSITIS

(PYOMYOSITIS)

The cause of myositis in the tropics is uncertain. If explored early no bact are found but later the pus contains staphylococci or streptococci. The dis usually occurs in malnourished persons. It has been thought that in s instances 'tropical phlebitis' may precede the myositis but pyomyositis oc frequently in New Guinea where tropical phlebitis is not encountered.

aphical Distribution. Most cases occur in tropical Africa, South America 'th Pacific Islands.

al Features. Pyomyositis starts with fever and induration of one or more rge muscles, mostly in the lower limbs. The indurated area subsequently tes and a large abscess may form and be associated with a swinging ture and leucocytosis. The affected area is swollen, hot and tender. When is superficial, fluctuation can be detected.

osis. This is usually not difficult except when the psoas muscle is involved. erential diagnosis includes Calabar swellings, scurvy and an underlying elitis. Staphylococcal pyaemia of other origin is characterised by us small abscesses. *Diphyllobothrium mansoni* in the larval stage, known arganum, may be found in an abscess in the muscles or subcutaneous in some endemic regions.

tment. The patient should be nursed in bed. When an abscess has formed, ld be aspirated and a suitable antibiotic given, but if resolution is delayed cess must be incised and the pus evacuated.

FIBROSIS OF THE LIVER PECULIAR TO THE TROPICS

rosis of the liver is frequent in underdeveloped countries where malnutrition ls and it appeared probable that a relative and absolute deficiency of n led to the cirrhosis either directly or indirectly by predisposing the liver to us agents such as toxins, parasites and viruses. It is now thought that dietary encies may only have a secondary role. Hepatotoxins, in herbs or contami- foodstuffs, of the pyrrolizidine group have been isolated as retrorsine and crotaline. Pyrrolizidine alkaloids have been shown, experimentally in als, to produce cirrhosis and hepatoma. Aflatoxins isolated from fungi minating grain used for feeding animals have also caused cirrhosis and toma experimentally. Infective hepatitis (p. **546**) is very common in the cs. Cirrhosis of the liver or lesser degrees of fibrosis may also arise in the itions described below.

Veno-occlusive Disease of the Liver

is disorder has been reported chiefly from Jamaica but it extends beyond Vest Indies and has been described in South Africa. The disease affects ns of all ages but most frequently children from 2 to 5 years of age. Its logy is still uncertain, but there is evidence that a poison in 'bush tea' infused plants, *Senecio* (ragwort) and *Crotalaria*, causes the disease in malnourished ren. Animals injected with extracts from these plants have developed similar ges in the liver.

Pathology. The acute stage of the disease shows occlusion of the centri veins by proliferation of the intimal cells and swelling of the subintimal This leads to back pressure atrophy of the liver cells and, if the patient s for some time, centrilobular fibrosis.

Clinical Features. The disease may occur in an acute form with rapid e ment of the liver and ascites but usually without jaundice and splenom death from hepatic failure may follow after a few days. However, with or out treatment, complete recovery is possible, or a subacute stage, with en ment of the liver but few symptoms of ill-health, may ensue. From th patient may gradually recover or the fibrosis may progress so that the becomes extensively cirrhotic with all the symptoms and signs of portal tension and hepatic failure.

Treatment. A well balanced diet with adequate animal protein must be and all forms of 'bush tea' excluded.

Indian Childhood Cirrhosis

This disease occurs in the children of strict vegetarians in India. The chi are not obviously malnourished, the majority being breast-fed and not belon to the poorest families. The incidence is predominantly in males between 1 3 years of age. As more than one case occurs in over 50 per cent of aff families, a sex linked genetic factor appears probable. There is no evidence dietary toxin. A defect of cellular ability to deal with the virus of infe hepatitis has been postulated.

Pathology. There is inadequate regeneration of hepatocytes, diffuse necros liver cells and replacement fibrosis. The degenerate cells appear as granular smudged eosinophilic masses. Fibrosis is of portal type involving small group cells with complete loss of normal hepatic architecture. The veins are unaffec The presence of α-fetoprotein in the serum has been reported. This may correlated with the defective hepatocytes.

Clinical Features. The disease may be fulminating, acute with death within to three months, or subacute nearly always proving fatal within one ye Enlargement of the liver is invariable and is accompanied in the majority splenomegaly, ascites and jaundice.

Treatment. This should be on the same lines as for infective hepatitis (p. **54**

Miscellaneous Causes of Fibrosis of the Liver

(Bantu Siderosis)

Iron. Hepatic cirrhosis associated with siderosis has been found amongst t adult Bantu of South Africa as well as in Ghana as a result of a dietary overlo (p. **128**).

a. Chronic malaria may cause a reaction in the liver with fibrous tissue n limited to the periportal region. However, in certain hyperendemic malaria sufferers from a severe degree of malnutrition and malaria have nd to have a diffuse fibrosis of the liver.

losis. In brucellosis granulomatous deposits occur in the liver and other out only rarely has cirrhosis of the liver been seen to develop in the of other aetiological factors.

-cell Anaemia. In sickle-cell anaemia the liver is often altered in structure tion as a result of the combined effect of anaemia, capillary obstruction es of sickle cells and distension of Kupffer cells with phagocytosed ytes. Focal necrosis, scarring and fibrosis of the liver are therefore often n sickle-cell anaemia (p. 130).

inthic Infections. Fibrosis of the liver in association with schistosomiasis clonorchiasis (p. 67) and fascioliasis (p. 69) is well recognised.

TROPICAL ULCER

aetiology of tropical ulcers is still in doubt. Predisposing factors are ry, minor injuries occurring in the presence of undernourishment, poor c surroundings and debilitating diseases such as malaria. The bacillus *cterium fusiforme* and the spirochaete *Borrelia vincenti* can usually be strated in the ulcer, but the part they play in its production is uncertain. mentally, discharge from an active lesion kept in contact with damaged has reproduced the ulcer in man. The disease is widely distributed in l countries, occasionally in epidemic form, particularly after a famine.

ology. The edges of the ulcer are raised, thick, oedematous and infiltrated eutrophils. In the early stages the ulcerated area is covered with necrotic nd the underlying tissue shows fibroblastic proliferation. Very severe cases how destruction down to the periosteum. Staphylococci and streptococci ually present in addition to *F. fusiforme* and *Bor. vincenti*.

ical Features. The initial lesion of a tropical ulcer is a bleb filled with neous fluid. It may be painful and itchy with some constitutional upset. he bleb ruptures, and a green-grey moist slough is exposed which rapidly s in the skin and subcutaneous tissue up to a diameter of 5 cm or more. w days these tissues slough and liquefy releasing a very offensive discharge. r extension may take place peripherally. After a week or more there is no further spread and the necrotic tissue separates, exposing an ulcer remains more or less stationary. In the chronic state the edges of the ulcer sed and slope down sharply towards the ulcerated surface. The damage limited to the skin and superficial fascia, but in severe cases deep struc- .g. tendons, nerves, blood vessels and periosteum, may be invaded. Bone y affected (although the ulcer over a sequestrum of chronic osteomyelitis may simulate a tropical ulcer). Tropical ulcers generally affect the par body exposed to trauma, especially the lower third of the leg and the f ulcer is usually solitary, but after healing no immunity is developed a recurrence.

General constitutional effects of a tropical ulcer are slight, and adenit found except as a result of secondary infection.

The ulcer heals slowly with a tissue-paper-like scar which may brea from very slight trauma. When the lesion has been severe enough to deeper tissues, scarring and deformity result; if near a joint it ma ankylosis. Carcinoma (epithelioma) sometimes arises in the edge of chronic tropical ulcer. These growths are usually of relatively low maligna regions where neglected tropical ulcers are frequent they constitute one more common causes of malignancy.

Diagnosis. The appearance and progress of an ulcer with few constit symptoms are characteristic. Isolation of *F. fusiforme* and *Bor. vinc* confirmatory. Early cutaneous diphtheria may be mistaken for a tropica but constitutional symptoms are severe and *Cl. diphtheriae* may be isola chronic ulcer of yaws or syphilis will be associated with a positive Wasse reaction and perhaps other signs of a treponematosis. Buruli ulcer is des below.

Treatment. Rest in bed with elevation of the affected part and a generou with adequate proteins are important. Local treatment consists in tho cleansing of the ulcer with hypertonic magnesium sulphate. Penicillin as (300,000 units) intramuscularly, repeated in 48 hours, or tetracycline 2 g da seven days gives good results. In very chronic cases, after cleansing and trea with antibiotics, excision of the ulcer and scar tissue may be required. followed by skin grafting.

Ambulant treatment, with the ulcerative area supported with strips of adh plaster, may be effective when rest cannot be enforced. The dressing is chang intervals of about five days. Antibiotics should be given.

Prophylaxis. Where tropical ulcers are a risk, abrasions should be cleansed covered without delay. The provision of a good diet, washing facilities and a aid service have abolished tropical ulcers from labour forces on well-run es in the tropics.

BURULI ULCER

This condition, first accurately described in Australia and New Guinea named from its frequency in Buruli in the Nile valley of Uganda, is caused by acid-fast organism, *Mycobacterium ulcerans*. The epidemiology is unknown the known foci of infection are consistent with the hypothesis that the envir ment in swamps following unusual flooding of rivers is of aetiological importa It is now recognised to begin usually as a single small subcutaneous noc situated commonly on the leg or forearm. The skin over the centre of the noc ulcerates and, untreated, the ulcer extends to involve a progressively large a

cally there is much necrosis of subcutaneous fat and *Myco. ulcerans* are
in the necrotic tissue in the base of the ulcer.
ected before ulceration, the nodule should be excised when healing
curs. Ulcers require to be excised and skin grafted. In addition drugs
in the treatment of leprosy have been employed, the most promising
fazimine (p. 23).

CANCRUM ORIS

um oris is now rarely observed except in poorly nourished children in the
It is characteristically preceded by an infective illness, especially a severe
of measles. The pathology is that of a rapidly developing gangrene,
g inside the mouth and penetrating through the lips and cheek resulting
disfigurement. Untreated it frequently causes death. However, with or
treatment, in those who survive the ulceration quickly becomes de-
d.

nt. In the acute stage parenteral fluids, usually including blood trans-
are to be administered. Food and vitamins are best supplied through a
tric tube. Penicillin or sulphonamides are highly effective in arresting the
An antimalarial is usually indicated and, exceptionally, at the onset a
steroid may be required. The gangrenous areas should be irrigated with
r a solution of glycothymol and gauze pads soaked in Eusol should be
to raw surfaces. Subsequently skilled plastic surgery may do much to
me the hideous defects.
ention depends on improved nutrition and hygiene in the community and
ful combating of infectious diseases.

BURKITT'S LYMPHOMA

e the original description by D. P. Burkitt in Uganda in 1958 there has
ncreasing interest in this particular form of malignant lymphoma, now
ised as the most common neoplasm affecting children in certain parts of
al Africa. The tumour has also been described from many other countries.

iology. In view of the demonstrated relationship between the incidence of
mour and climatic factors of temperature and rainfall, it was assumed that
biological agent must be implicated. Since the geographical distribution of
nour corresponds to that of several insect vectors it was postulated that an
rus might be the causative agent. The subsequent recognition that large
of the moist tropics were free from this tumour necessitated a modification
concept, and it is now postulated that the high incidence in certain areas
e the result of changes in the lymphoreticular system caused by persistent
a. It is suggested that an ubiquitous virus, possibly the Epstein-Barr virus,
ce of which can be found in all patients with this tumour, tends to produce
stic change more frequently when acting on cells already altered by
c malaria.

Pathology. Extensive studies have shown that this tumour is a m lymphoma of poorly differentiated lymphoblastic type. The histological is of uniform masses of immature lymphoid cells. Interspersed between th are many large clear histiocytes with poorly staining cytoplasm whi contain cell debris. The so-called 'starry sky' pattern seen in section tumour is due to these large histiocytes. Cellular detail is more easily s interpreted in the stained imprint preparations from fresh unfixed tissues, ordinary histological sections.

Clinical Features. In Africa this tumour has a peak incidence between t of 4 and 8 years. Relatively few cases occur after puberty, but occasion are seen in adult life. The most frequent presenting feature is a tumour mandible or maxilla. The first clinical sign is usually loosening of the mo pre-molar teeth which eventually become displaced, distorted and lost tumour grows. Tumours of the maxilla may present as exophthalmos due t invasion of the orbit. The eye may eventually be totally destroyed and stage it is difficult to distinguish this tumour from a retinoblastoma. A parti characteristic feature is the tendency for the tumours in the jaws to be m and it is not uncommon for all four jaw quadrants to be involved simultane

The second commonest clinical presentation is an abdominal tumour, u caused by involvement of the kidneys, adrenals, ovaries, liver or abdc lymph nodes. Involvement of the kidneys, adrenals and ovaries is often bil

The third commonest presenting feature is paraplegia which is of sudden flaccid from the outset and associated with incontinence of urine and f without radiological evidence of vertebral collapse.

Other sites characteristically involved in this multifocal tumour are the bones of the limbs, the thyroid and salivary glands, the testes and the Bilateral massive tumours of the breasts sometimes develop in young adult wc

The rarity of peripheral lymphadenopathy is particularly characteristic.

Treatment. This tumour is unusually sensitive to a large range of cyto drugs and to radiotherapy. As the tumour is probably always multif systemic chemotherapy is preferred. The best results to date have been obt with cyclophosphamide and orthomerphalan. The former is given in single doses of 30 to 40 mg/kg body weight repeated on one or more occasions recovery of marrow depression. The latter is given in one or two doses of 1 1·4 mg/kg. A more extensive regime using multiple drugs has been used success in resistant tumours. Intracranial involvement, recognised by the pres of tumour cells in the CSF, should be treated with methotrexate. In some cl in Africa prolonged survival rates of over 30 per cent have been reported.

IDIOPATHIC MULTIPLE HAEMORRHAGIC SARCOMA OF THE SKIN

(KAPOSI'S SARCOMA)

This strange multiple neoplasm in skin, first described in Europe in 1 which is rare in Europe and America, is now known to be relatively commo rts of Africa. It predominantly affects men. The aetiology and the or its geographical distribution and sex and age incidence are unknown.

ogy. The tumours of the skin are well defined nodules which consist of od vessels and large spindle cells with numerous mitotic figures. Pigment free in the tissue or within histiocytes are easily seen. Strands of ve tissue, infiltrated with plasma cells and lymphocytes, run through the The peripheral lymphatics are often markedly dilated. At autopsy lesions can be demonstrated in almost all tissues except the brain but ve rise to symptoms.

al Features. Vague paraesthesiae, local sweating or oedema may precede earance of nodules in a proportion of cases but the appearance of a nodule kin of one limb is the first important diagnostic feature. The nodules vary rom 2 to 20 mm in diameter. They are blue or brown in colour, firm and to touch and have a smooth surface. The appearance is highly charac- They may coalesce, ulcerate and become infected, followed by over- of granulation tissue. In order of decreasing frequency nodules occur in n of the feet, legs, hands, arms, trunk, genitalia, head and neck.

ph nodes are enlarged in half the cases but they are not usually invaded by mour. Oedema is common, varying from slight local swelling to gross ement of a whole limb. The latter indicates involvement of the deeper soft and bone.

nique feature is spontaneous regression and complete disappearance of dual nodules although the disease as a whole may be progressing.

gnosis. The condition is suspected from the striking clinical picture and reveals the characteristic histology. Radiological studies by soft tissue may show unsuspected nodules throughout an affected limb, and bony s are demonstrated as generalised or localised rarefaction, loss of trabecula- cortical erosion or cysts.

gnosis. The condition is slowly progressive and ultimately fatal in an ge time of eight years, but occasionally the course is rapid and fulminating.

eatment. The tumours, although radiosensitive, may be too widespread for ive radiotherapy. High voltage therapy throughout the depth of a limb is lly required, since superficial irradiation is only of value for the early rficial nodules. As radiotherapy is not available in many parts of Africa and ry can offer only limited benefits, chemotherapy is the treatment of choice. ra-arterial regional perfusion of the limb or limbs with nitrogen mustard or cytotoxic drugs has caused improvement in a proportion of cases. Regres- of the disease may be prolonged by the oral administration of 0·5 mg of quone twice a week. These effects are however only transient and palliative e more severe and malignant forms of the disease.

EPIDEMIC DROPSY

(ARGEMONE POISONING)

This disease is due to the use of mustard oil contaminated with the se poppy weed, *Argemone mexicana*. The weed grows commonly in mustar and contains a toxic alkaloid, sanguinarine. This substance interferes w oxidation of pyruvic acid, which accumulates in the blood and tissues patient. Epidemic dropsy occurs in groups of people partaking of the sam especially curried rice prepared with contaminated mustard oil.

Geographical Distribution. Epidemic dropsy is encountered in India, esp in Bengal, Bihar, Orissa, Madhya Pradesh and Uttar Pradesh. Cases ha been noted among Indian expatriates in Fiji.

Pathology. There is general dilatation of the smaller arterioles and capillaries, especially those of the skin, heart muscle and uveal tract. New vessels in the deeper layers of the skin and mucosa may form haemangiom the cutaneous and mucosal surfaces. On examination of the deeper organ tissues widespread vascular dilatation and oedema are found.

Clinical Features. The onset may be gradual or acute, affecting a gro people taking the same diet. A period of ill-health with nausea, vomiting diarrhoea often precedes the onset of the oedema which appears first in the and feet and is accompanied by symptoms of cardiac failure. Fever accompanies the early stage of the illness. In severe cases the pulse is rapid may be irregular, and signs and symptoms of severe cardiac failure develo death occurs it is usually due to heart failure. An erythematous mottling of skin may follow the oedema, and haemangiomatous tumours up to 1 cm diameter may appear in the skin or mucosal surfaces. Bleeding from these a slight trauma is easily controlled by local pressure. Glaucoma is a seri complication.

Diagnosis. During an outbreak the diagnosis is easy from the dietetic hist and clinical findings. In contrast to the oedema of beriberi there are no companying features of peripheral neuropathy and there is no response thiamine. Famine oedema attacks those who have been subjected to severe fo restriction and who are usually emaciated and hungry.

Treatment. For the affection of the heart, rest in bed is essential and the inta of salt should be restricted. A high protein diet must be given and all contan nated mustard oil excluded. The addition of vitamin B complex to the diet advisable. Improvement is often slow and convalescence protracted. Wh ocular tension is increased, surgical treatment is usually required to relieve t tension.

Prevention. Steps should be taken to prevent contamination of mustard cro with the weed *A. mexicana*. A test should be carried out to detect this contamina in mustard oil.

VOMITING SICKNESS OF JAMAICA

(Ackee Poisoning)

illness is attributed to the eating of unripe fruit of a common West and South American tree, *Blighia sapida*. The mature fruit is wholesome ipe fruit is believed to contain hypoglycin, a water-soluble toxin.

cal Features. Only children from 2 to 5 years of age who are undernourished cted. The first symptom is vomiting, and after an interval this is followed vsiness, going on to convulsions and coma. In the late stages of the illness marked hypoglycaemia which may be due to hypoglycin blocking gluco- esis in the liver.

tment. If started early, continuous intravenous glucose can bring about ry. Without treatment the mortality rate is high.

SUBACUTE MYELO-OPTICO NEUROPATHY

ondition, also known by the abbreviation, SMON, consists predominantly nal degeneration of peripheral nerves and spinal tracts, usually bilaterally etrical; frequently the vagus nerves and, less commonly, the optic nerves ffected. Many cases occurred in Japan and a few have been reported from ralia and elsewhere. There is a strong association with the preceding ingestion ioquinol in large quantities, prescribed for dysentery. It seems, therefore, opriate to record the syndrome as a warning against the use of clioquinol, ugh other agents, such as local viruses, may well be additional aetiological rs. The banning of clioquinol in Japan was followed by the virtual dis- arance of the disease in that country.

EFFECTS OF LIGHT AND HEAT

Exposure to Strong Sunlight

nburn is caused not by the heat of the sun but by ultraviolet light. The skin ose with fair complexions is especially sensitive to strong sunlight. Natural ance to the sun can be won by gradual exposure which enables the skin to ire protective pigmentation.

linical Features. Short periods of exposure to unaccustomed strong sun uce only erythema and itchiness of the affected area of skin. Should, how- , the exposure be prolonged, acute pain and oedema with vesicles and bullae develop in the affected part. These local changes are accompanied by ral malaise, headache and nausea. Severe cases may suffer from prostration even some cardiovascular failure. When a large area of skin has been aged, this may interfere seriously with sweating and predispose to heat rpyrexia.

Treatment. For mild sunburn no treatment is needed, but for severe treatment in bed in a cool room is required with sedatives to relieve the pai features of shock and dehydration must receive the appropriate trea Large blisters should be pricked, and calamine lotion containing 0·5 pe crystal violet should be applied. Antihistamine drugs given by mouth h relieve pruritus.

Prophylaxis. Untanned skin should be exposed to strong sunlight onl short graded periods. Some protection is afforded by face powders and cr containing para-aminobenzoic acid which absorbs ultraviolet light.

Solar Keratosis

After prolonged residence in the tropics atrophic patches are liable to de on exposed parts of the body especially in those with fair skins. The backs o hands, the neck and the forehead are most commonly affected. These areas later develop small patches of hyperkeratosis which occasionally progress t formation of squamous celled carcinomata. This process is seen with maxin severity in albinos in the tropics.

Treatment. The skin should be protected as far as possible from the sunligh clothing and creams. Hyperkeratotic areas can be removed by the application one week of 5 per cent fluorouracil ointment under an occlusive dressing.

Acclimatisation to Heat

In cool climates heat production in the body is balanced by loss from surface chiefly by radiation and convection. The hypothalamus controls superficial circulation and produces vasoconstriction or dilatation as requi for the conservation or loss of body heat. When, however, the atmosphe temperature is above that of the body, then evaporation of sweat is all-importa in the maintenance of a stable body temperature, assisted to a minor degree insensible loss through the skin and lungs.

Acclimatisation to heat is an essential preparation for workers exposed excessive heat in certain industries in cool climates as well as for people who li in the tropics. This can be achieved by undertaking exercise daily under artificial produced or natural hot weather conditions for 10 to 14 days, by the end which time the body metabolism will have become partially adjusted. As tl result of this adjustment an increase in the total volume of circulating flu compensates the body for the expanded vascular bed, and this is accompanied b a diminished pulse rate and an increased cardiac output. Further, the sa excreted by the kidneys is decreased and in addition the concentration of salt i the sweat is much reduced, mainly as a result of increased activity of the adren glands with enhanced production of aldosterone. The sweat glands also becom more active, responding more rapidly and efficiently to any increase in bod temperature; consequently the rise in body temperature in response to exercis diminishes. With these adjustments the individual is better able to work an remain well under conditions of high atmospheric temperature provided a

te intake of water and salt is maintained. In contrast, exposure to adverse
ons or the taking of cholinergic drugs may produce cessation of sweating
ailure ('fatigue') of the sweat glands.

Prickly Heat

ny Europeans living in the tropics, especially when humidity is high, suffer
prickly heat. Some become acclimatised, while others continue to be
ed by it throughout the hot season. The condition arises from blockage of
ducts within the prickle cell layer of the epidermis. As a result of this
age, sweat escapes into the epidermis and causes severe irritation. The
s produced consist of numerous minute papules, surrounded by erythema
ria rubra) which become vesicular or pustular (miliaria pustulosa). These
te pustules usually contain sterile pus, although scratching may lead to
dary pyogenic infection of them. The lesions of prickly heat are most
rous in parts of the body in close contact with clothing, e.g. around the
, shoulders or wrists, but they also occur on exposed areas such as the
s of the hands. The lesions are very prickly and irritating and, if extensive,
great discomfort and may be followed by tropical anhidrotic asthenia.
ting due to any cause aggravates the symptoms.

eatment. The principles of treatment are to reduce sweating to a minimum
to overcome the blockage of the sweat ducts. If the patient can be transferred
cool environment such as an air-conditioned room, the blocked ducts
me patent within a week or two. The general measures prescribed below
er prophylaxis should be instituted. The skin should be washed gently and
sparing use of a bland soap containing hexochlorophane is helpful. In severe
s, when artificial cooling cannot be maintained, the application of anhydrous
line will restore the patency of the sweat ducts. When irritation is intense
ef should be given by the administration of a sedative, such as phenobarbitone,
ng every six hours.

rophylaxis. It is important to avoid plugging the orifices of the sweat ducts.
refore maceration of the skin by sweat or liquid applications, excessive
hing and irritation from clothing (either by friction or a chemical contami-
t) must be avoided. The use of a bland soap containing hexochlorophane is
ocated. Dusting powders should only be lightly applied. Clothing must be
e fitting, changed frequently and thoroughly rinsed after washing. Controlled
ning of the skin with sunlight may help acclimatisation. The diet should be
as does not lead to capillary dilatation and excessive sweating. Curries,
diments and alcohol should be taken only in moderation, if at all.

Heat Syncope

eat syncope or fainting is not uncommon in people dressed in unsuitable
nes in a warm atmosphere with poor air circulation, at exercise, on suddenly
ding up, after standing still for a considerable time, or even at rest. Fainting
nen due to an expanded vascular bed with an inadequate compensatory

increase in blood volume and insufficient cardiac output. This results in a s drop in blood pressure which leads to temporary cerebral anoxia.

Treatment. The patient is put to rest lying down (the head low and th raised) in a cool atmosphere and unnecessary clothing loosened or remo

Heat Exhaustion

Heat exhaustion is often brought on by a period of great heat or by effort under conditions of hot weather, when the patient has not taken en fluid and salt to balance the increased loss by sweating. The amount of flui as sweat during a working spell under these conditions may be as much as even 8 litres and even in persons fully acclimatised to heat this may entail a of approximately 2 g sodium chloride per litre of sweat. Ill-health, espec gastrointestinal disturbances with vomiting and diarrhoea, will increase the of heat exhaustion.

Clinical Features. There are usually warnings which should be recogn These include headache, giddiness, loss of appetite, nausea, muscular cra especially of the legs and feet, and personality changes—irritability and lac co-operation. If the disorder is recognised at this early stage, removal to a atmosphere and cool water to drink, with salt as required, will soon restore patient to normal. If, however, it is not recognised and if treatment is dela the results are less satisfactory. In an established case of heat exhaustion patient is distressed and anxious, with a pale sweating skin, rapid weak pulse low blood pressure, and often complains of cramps. Although the surface is c the rectal temperature may be slightly raised (the 'cold moist man'). Dehydra is usually marked and no chlorides can be found in the high coloured sca urine, indicating that there is a depletion of both salt and water. When hydration is limited to loss of extracellular fluid there will be no thirst a consequently a considerable degree of water depletion may exist with producing any symptoms. The importance of water depletion must be stress Adequate salt replacement, however, is also essential.

Treatment. In severe cases it is usually not possible to give the required amou of fluid and electrolytes by mouth. Intravenous infusion of saline is theref needed, the quantity and composition depending on the degree of dehydrat and electrolyte deficiency (p. **186**). Useful practical guidance to the requirem of sodium chloride can be obtained by testing the output of chloride in the uri Initial and maintenance treatment should be carried out in a cool place u convalescence is complete. When heat exhaustion is not recognised and treat the patient may develop a high temperature and pass into a condition secondary heat hyperpyrexia (p. 117).

Tropical Anhidrotic Asthenia

The majority of patients with this disorder have suffered from prickly h This has left extensive areas of skin, especially on the trunk and limbs, incapa ting properly. The condition develops insidiously towards the end of the ather, with headache, giddiness, lack of energy, diminished sweating and narked polyuria, the dilute urine containing chloride. A rise of body ature is common and may occasionally reach hyperpyrexia. The plasma les are usually only slightly decreased.

onged treatment is needed. The patient must live in a cool climate until the is recovered and sweating has returned to normal; this may take up to two s.

Heat Hyperpyrexia

it hyperpyrexia occurs in those exposed for considerable periods to ally high atmospheric temperatures, independent of exposure to direct ht. Unacclimatised people are more liable to suffer, but a prolonged period ry high temperature may affect even those who are fully acclimatised, ling the local inhabitants. The disorder is always associated with cessation eating, and then the body temperature may reach 42° to 43° C or even r. Predisposing factors are those which interfere with the production and ration of sweat—unsuitable clothing and poor working conditions with air movement, heavy work in conditions of high temperature and humidity fever especially when due to malaria, pulmonary or renal disease. Diffuse ns of the skin, especially if treated with oily preparations and protective rings, may inhibit sweating and induce heat hyperpyrexia. Individuals with enital absence of sweat glands are particularly vulnerable. Alcohol and in drugs like atropine may play a part. Operations, particularly thyroid- my, may be dangerous. Hyperpyrexia may follow heat exhaustion when the dration leads to cessation of sweating.

athology. The most important changes are in the central nervous system. re is general congestion of the brain with increased pressure of the cerebro- al fluid. Microscopic examination may show degeneration of nerve cells, ticularly in the hypothalamic region and base of the brain.

linical Features. In primary hyperpyrexia the onset is usually dramatic with warning in a person who appears to be neither dehydrated nor deficient in though occasionally the patient may have noticed that perspiration had ome much less. He may have retired to rest feeling quite well and be found in na a few hours later. Loss of consciousness may be preceded by prodromal s of cerebral irritation. On examination a dry burning skin is found (the 'hot man'). When the temperature, which must always be taken rectally, reaches veen 41° and 42° C unconsciousness supervenes and without energetic tment the mortality rate can be 50 per cent. Heat hyperpyrexia may be iplicated by peripheral circulatory failure or acute renal or hepatic failure. morrhages are a frequent feature. After death the temperature may continue ise.

n cases of secondary hyperpyrexia the early symptoms are those of heat austion or tropical anhidrotic asthenia. If the patient is not treated, the perature continues to rise and the state of hyperpyrexia supervenes.

Diagnosis. Heat hyperpyrexia is likely during any prolonged peri unusually hot atmospheric conditions. Any patient with an unduly high tem ture and dry skin should be treated as such a case, care being taken to e other diseases, especially *P. falciparum* malaria by a careful blood examin A neutrophil leucocytosis is present. Lumbar puncture will exclude meni and at the same time will relieve the increased cerebrospinal fluid pressu frequent in heat hyperpyrexia.

Treatment. The aim is to reduce the temperature as quickly as possible in to prevent permanent damage to vital structures. This is done by lo wrapping the patient in a cool wet sheet and promoting evaporation by fan Concurrently parenteral antimalarial therapy (p. **968**) should be given if ma is a possibility. As the temperature falls, provided that the brain has not irreparably damaged, consciousness returns. Cooling should be stopped the rectal temperature has fallen to around 39° C, otherwise the tempera which goes on falling, may reach excessively low levels. As anoxia is freque present oxygen should be given. Chlorpromazine should be administered an adequate airway maintained. When return to consciousness is delayed, lum puncture and withdrawal of excess fluid may help. In the presence of circula failure intravenous hydrocortisone may be life saving. For the treatment of a renal or hepatic failure see pages **610** and **563**. During convalescence contro body temperature will remain unstable.

When hyperpyrexia is secondary to heat exhaustion, dehydration is usu severe. Therefore, in addition to reducing the high temperature, adequate w and salt replacement is essential.

Depending on the duration and degree of hyperpyrexia, the patient m recover completely, be left with residual brain damage or fail to respond treatment.

Prevention of Ill-effects of Heat

Careful selection should be made of those required to work under hot atm spheric conditions. General physical fitness and mental stability are importa people in the younger age group are, as a rule, more suitable for such emplo ment. Fever, gastrointestinal upsets, alcoholic excess and lack of sleep all p dispose to ill-effects of heat. It is highly important that the skin should be healt and that sweating should be normal.

When the atmospheric temperature is very high, leading to excessive sweatin even the fully acclimatised require to take extra fluid and salt. A daily intake up to 15 litres of cool drinking water and 30 g of sodium chloride per person m be needed to prevent water and salt depletion. Advice and encouragement required if such large amounts of fluid are to be taken. The extra salt is tak with food and in the drinking water, but it can, when necessary, be supplied enteric coated tablets. A total of 30 g of sodium chloride is supplied by addin 3 flat teaspoonfuls of salt or 18 enteric coated tablets, each containing 650 m of salt, to the normal daily intake of fluid and food.

In addition, everything possible should be done to improve working condition by arranging for a free circulation of air and for a reduction of high temperatur and excessive atmospheric humidity by air-conditioning. Clothing should be ligh se fitting. Hard or prolonged manual work should not be undertaken tmospheric conditions are exceptionally unfavourable. Off-duty living ns should be made as cool and comfortable as possible.

TROPICAL SPRUE

e is the name which the Dutch in Java gave to a tropical disease in which senting features are sore mouth, fatty diarrhoea and associated secondary stations of subnutrition and malnutrition. The cause is unknown.

ough delayed and defective absorption of fat is the abnormality most ecognised, the absorption of water, sodium chloride, glucose, vitamins nerals is also impaired (see below). The absorption of amino acids is less d and the excretion of pancreatic enzymes is normal.

ology. The disease is widespread in the tropics, especially in parts of Asia ing Sri Lanka, Southern India, Malaysia, Indonesia, Hong Kong and China. occurs in the Middle East, in certain of the Caribbean Islands and in America but is extremely rare, if it occurs at all, in tropical Africa. It frequently in Europeans and in Indians; it is also seen in Malays and beans of Spanish descent, but is rare in Chinese. It has also been reported erto Rico, but whether these patients had sprue or nutritional megalo- c anaemia is not clear (see below). In so far as epidemiology is concerned may be considered under four headings.

OUP 1. In the century before the Second World War tropical sprue as it red in Java, Hong Kong, Singapore and Colombo was a disease which ared to be largely confined to Europeans, usually of middle age, most of n had lived many years in the tropics and who were financially well off ared to the local inhabitants because of their professional and business nes. The disease occurred sporadically and usually developed insidiously was notable for remissions and relapses, often for no obvious reason. A n to temperate climates usually caused a remission but relapses occurred etimes after many years' absence from the tropics. Epidemics of sprue were reported but the occurrence of sprue in successive residents in a particular e (sprue house) suggested an infective cause.

ere is no doubt that the incidence of tropical sprue in Europeans resident in mic areas in Asia such as Colombo and Singapore is much less than erly. During this period of falling incidence there has been a great increase e number of refrigerators in shops, hotels and private houses, and also of industrial cold storage plants. Whether this reduced incidence of sprue is to improved hygiene consequent upon the increased use of refrigeration or her the quality of foods, both imported and home grown, has been bene- ly influenced is a matter of conjecture. The primary cause of this pre-war of sprue has never been elucidated and no specific agent, toxic, infective or tional, has been found.

OUP 2. Sprue in Puerto Rico is a disease which has been known for a long ; it affected the poorest inhabitants, whose diet was grossly defective in many respects. The megaloblastic anaemia which was present in many ca shown by Spies many years ago to respond dramatically to folic acid, wh recently been synthesised, with corresponding beneficial effects on the intestinal and other clinical features. Sprue in Puerto Rico was believed b to be a primary nutritional deficiency disease due mainly to folic acid defi More recently American military personnel in Puerto Rico have dev tropical sprue in spite of consuming an excellent diet. The question th arises whether sprue in American soldiers in Puerto Rico is the same dise occurred in the grossly malnourished poor inhabitants.

GROUP 3. During the Second World War when hundreds of thousa troops went to S.E. Asia sprue was reported to have occurred in epidemic in British and Indian soldiers, some of whom had only been in the area fo or weeks. They had previously been eating excellent Army rations and much younger in age than those classical cases of sprue in group 1. The ons often sudden in contrast to the insidious onset of group 1.

GROUP 4. Baker described a large epidemic of sprue in Indians in 1961- Vellore, Southern India. This epidemic has subsided but the disease is endemic in that area. The cases had the classical features of sprue. Despit obvious suggestion that an epidemic of this size must have an infective basi specific organisms were found, but the possibility remains that it was d some unidentified virus. Since the Indian population in South India has partaking of a notoriously poor diet for a long time and since no change i diet occurred during the epidemic or after it had ceased, the view that this of sprue was primarily due to dietary deficiency received no support.

The view that tropical sprue is a specific nutritional disease primarily d dietary deficiency of folic acid cannot be sustained for several reasons.

Thus it has been fully substantiated that severe nutritional megalob anaemia due to folic acid deficiency is of common occurrence in tropical A where tropical sprue is virtually unknown. Likewise the megaloblastic ana of pregnant women which is a common disorder in many parts of the wor primarily due to folic acid deficiency but fatty diarrhoea is not a feat Hence it must be concluded that the clinical features of sprue are prima the result of malabsorption due to some as yet unknown cause or causes.

This primary defect in absorption may be increased by any associated bacte gastrointestinal infection or change in the pattern of the bacterial flora of small intestine. An attack of sprue frequently follows upon bacillary dysenter other gastrointestinal infections, but the aetiological association with t diseases has not survived statistical analysis.

Once deficiency of folic acid has occurred, a vicious circle may be comme as folic acid is required in large amounts by the intestinal cells if the effete of the small intestine are to be rapidly replaced by new cells. In other words acid deficiency may well be an important factor in maintaining or increa intestinal malabsorption.

It is difficult to understand why the administration of antibiotics may imp the intestinal features of sprue either when given alone or as a suppleme folic acid therapy, since no specific organisms which could be killed by

c have been incriminated as the cause of sprue. Perhaps the effect is
o that produced in the blind loop syndrome (p. **494**) in which organisms
tamin B_{12} to their own use and thus make the patient deficient in this
If sprue is due to a virus it seems unlikely that it would be killed by any
ic at present available.

iscovery that wheat-gluten is the agent responsible for coeliac disease
nteropathy) indicates the possibility that some constitutional inability to
h certain nutrients may be important. Thus it has been suggested that the
tion of the geographical location of tropical sprue in Sri Lanka, India,
ia and China and its absence in Africa, may be correlated with the foods
ncluding the type of fat used for cooking, in these regions.

nts with tropical sprue are not sensitive to wheat-gluten and its with-
from the diet produces no clinical benefit.

clinical and biochemical abnormalities and the radiological and histo-
changes in the small intestine in sprue are not specific for that disease,
mparable findings are present in other malabsorptive disorders such as
disease (gluten enteropathy) and non-tropical sprue (idiopathic steato-
).

n what has been said it may be concluded (1) that the cause of tropical
s not known and (2) that the condition may be a clinical syndrome rather
disease entity.

iology. The pathological changes closely resemble those of wheat-gluten
vity, although they tend to be less advanced. The jejunal villi are blunted
ly absent and there may be a subepithelial cellular infiltration with plasma
nd lymphocytes. This appearance, called partial villous atrophy, is a non-
c change and may be found in other diseases of the small intestine with
rrhoea. The abnormality appears to be confined to the jejunum in early
but later also affects the ileum.

stores of vitamin B_{12} in the body are much greater than those of folate,
bly enough for two to three years. As this vitamin is absorbed from the
ileum, which is much less affected in sprue than the jejunum, a deficiency of
in B_{12} takes longer to develop and is encountered only in sprue of long
ion. A macrocytic anaemia is common in sprue and in many cases megalo-
ic change is present in the bone marrow. In the earlier stages of the disease
appears to be due to folate deficiency alone. When malabsorption has
nued for weeks or months deficiencies of other vitamins such as A, D and K
riboflavin may result. The clinical and biochemical signs of depletion of
r and minerals, including especially iron and calcium but also sodium,
sium and magnesium, may also be present.

nical Features. The condition can present in any grade of clinical severity.
ough the onset may be acute and occur within a few weeks of arrival in the
cs, it is more often insidious with increasing lassitude, mental apathy and
ssion, loss of weight, anorexia, flatulence and dyspepsia. Remissions and
ses which occur for no obvious cause are a characteristic feature. Initially or
some weeks a watery explosive diarrhoea occurs which in some cases
rs to have been precipitated by a gastrointestinal infection or by dietary or

alcoholic indiscretion. Later, up to 10 pale loose foul-smelling stools passed daily, especially in the morning or during the night. Defaecation is follows meals and the stool is bulky, frothy, floats in the lavatory pan difficult to flush away. Vomiting may occur with nausea, abdominal dis and borborygmi. After some time the tongue becomes sore, first at the edges, the discomfort being increased by smoking or taking hot spicy fo curries; it becomes fiery red in colour and painful. Later the whole mou throat feel sore and there may be difficulty in swallowing. Nocturnal u frequency and in women amenorrhoea have been noted.

In the untreated chronic disease there is much loss of weight, the tor clean and shiny from atrophy of the filiform papillae and fissures may de Abdominal distension, pallor and generalised pigmentation appear. Th becomes coarse and dry (follicular keratosis) possibly due to deficier vitamin A (p. **135**). Fever is uncommon unless associated with severe m blastic anaemia or with superadded infection, often of the urinary tract. tinued malabsorption of vitamins of the B complex leads to glossitis, ch and angular stomatitis (p. **162**) and rarely lack of absorbed vitamin K ca tendency to bleed into the skin or from the mucous membranes (p. **764**). Ble haemorrhoids may be a feature and complicate the appearance of the s Loss of fluids and electrolytes may lead to severe dehydration, muscular wea and cramps, and lack of vitamin D and calcium to osteomalacia and te Oedema of the extremities may be a feature of the chronic disease. Perip neuropathy is very rare.

Diagnosis. The clinical features and the history of residence in an area r for tropical sprue will suggest the correct diagnosis if care is taken to reco the early and the mild cases as well as the late presentations. Evidence of absorption is obtained by estimation of the faecal fat (on an ordinary ward not more than 7 g of fat is passed daily by the normal person, p. **489**), by th glucose tolerance curve (p. **684**) and by the abnormal d-xylose tolerance (p. **489**). After a 25 g loading oral dose the normal person excretes 25 per ce the urine within five hours. This is also the case in patients with pancre steatorrhoea. In contrast, in sprue and wheat-gluten induced enteropathy percentage excreted is reduced. If the 25 g dose causes nausea or vomiting a loading dose may be used instead.

The anaemia, when present, is usually macrocytic and the bone mar megaloblastic, but it may also be hypochromic from defective absorption of i in which case a dimorphic anaemia is produced (pp. **727**, **730**). Altho temporary achlorhydria is not uncommon in sprue it is not usually histar fast. If free acid is present in the gastric juice after the injection of pentagas pernicious anaemia can be excluded.

Intestinal anatomy is assessed by barium X-ray examination (p. **437**) u non-flocculable barium, and by intestinal biopsy (p. **440**). The histolo appearance is that of villous atrophy and neither this nor the radiological s are specific for tropical sprue but merely indicate that a malabsorption syndr is present.

Differential diagnosis is from other forms of steatorrhoea such as chr pancreatitis, wheat-gluten enteropathy (coeliac disease), idiopathic steatorr pical sprue), regional ileitis and tuberculous enteritis. Lymphoma of the testine, pernicious anaemia, gastric carcinoma and Addison's disease o have to be considered. Malabsorption may also result from heavy ns of the intestine with *Giardia intestinalis*, *Strongyloides stercoralis* or *ia philippinensis*. Intestinal hurry as part of an allergic response in the ages of ancylostomiasis may suggest the onset of sprue (p. 72). Early ms of sprue may erroneously be attributed to amoebiasis or a neurosis.

ment. Complete rest in bed is required initially for the severely affected If diarrhoea is severe a preparation of codeine may be required arily. In addition dehydration must be corrected and supplements of um may be required. For the patient with disease of recent and acute 0 mg of folic acid is given intramuscularly daily for three days. In n 5 mg is given orally twice daily for at least one month after all symptoms isappeared. This normally produces a dramatic clinical response with improvement in glossitis, stomatitis, steatorrhoea and other clinical s. If the bone marrow is megaloblastic there is a brisk haematological se with reticulocytosis and reversion to normoblastic bone marrow. Serial biopsies have shown that in recent cases the jejunal mucosa soon returns nal following folic acid therapy. Such a patient can continue to live in the and remain well. It has not yet been established whether to give a small ylactic dose of folic acid daily to prevent a relapse in patients remaining in pics or to administer folic acid only if a relapse occurs.

ntreated sprue has been present for more than six months steatorrhoea will in about a quarter of the patients for a variable period despite treatment olic acid, but this will usually respond to a course of antibiotics. For this se 1 g tetracycline daily for 7-14 days should be given. If there is no nse, 2 g chloramphenicol daily for five days should be tried.

ne patients suffering from long continued chronic sprue may not respond c acid because of severe deficiency of vitamin B_{12}. These patients should be intramuscular injections of hydroxocobalamin, 1000 micrograms twice in eek, followed by a dose of 250 micrograms once a fortnight for six weeks in ion to folic acid. By this means the anaemia is corrected and the danger of oping subacute combined degeneration of the spinal cord is avoided.

hypochromic anaemia due to iron deficiency is present, ferrous sulphate be given. In severe cases a multivitamin preparation containing 10 mg nin, 5 mg riboflavin and 50 mg nicotinamide twice daily should be ribed for a few weeks. In addition phytomenadione (Vitamin K_1) (p. **765**) e required if there is a tendency to bleed. Tetany necessitates the giving of um parenterally and vitamin D by mouth.

mplicated diets are no longer required but the diet initially should be bland ppetising, limited in fat and carbohydrate and high in protein. Because of high content of folic acid and other vitamins the importance of liver, meat green vegetables in the diet must be stressed after recovery. Folic acid ements should always be given to women who have had sprue should they ne pregnant.

FREDERICK J. WRIGHT.
Sir JAMES BAIRD.

Anaemia in the Tropics

In many tropical countries anaemia is common and often severe. This is explained by the high frequency of protozoal, helminthic and bacterial in and the prevalence of malnutrition. It cannot be emphasised too strong the aetiology of anaemia in the tropics shows great variation from one cou another, and from one area to another, and effective management ca follow the clear appreciation of local patterns of disease, nutrition anc custom. It is not the purpose of this chapter to describe those causes of a also seen in temperate climates. These are covered adequately in the dealing with disorders of the blood in Davidson's *Principles and Prac Medicine* (pp. **713** to **767**). The reader is referred to the chapter dealin nutritional diseases for information regarding nutritional deficiency as a ca anaemia (pp. **165** to **166**).

IRON DEFICIENCY ANAEMIA

ANCYLOSTOMIASIS. This is a major cause of iron deficiency anaemia. worm ingests between 0·03 and 0·15 ml of blood per day: hence the loss of in a heavy infection (over 1,000 worms) is large, and anaemia develops ra after the iron stores are exhausted. Folic acid deficiency may complica anaemia if the dietary intake is inadequate for the demands of increased re formation. Where the blood loss is severe protein deficiency may also ap However, this last complication is unlikely to occur in the face of reaso nutrition and adequate liver function. If the anaemia is treated with ir rapidly improves, but will return when iron therapy is stopped, unless dewor is undertaken. It follows that deworming is essential in treating the ana (pp. 71 to 73).

Because of the mode of infection, ancylostomiasis predominantly a agricultural communities. Hookworm infection sufficient to cause anaemia not usually occur in children under 2 years of age.

All the usual features of iron deficiency anaemia, namely angular stoma glossitis and koilonychia may be seen and kwashiorkor may complicate picture (pp. **722** and **118**).

The aetiology, prevention and treatment of ancylostomiasis is describe pages 71 to 73.

MEGALOBLASTIC ANAEMIA

Although Addisonian pernicious anaemia (p. **728**) occurs in all races, relatively uncommon in tropical countries, where megaloblastic anaemia is more frequently due to nutritional deficiency of folic acid or vitamin B_{12} requirements of both these substances are increased during growth, pregn infections (including malaria) and when there is increased red cell formati lytic anaemia. Generally, in this respect the available body store of folic nore vulnerable to depletion than that of vitamin B_{12}, hence most of megaloblastic anaemia in the tropics are due to folic acid deficiency. nimal protein is nearly or completely absent from the diet, vitamin B_{12} y may occur.

osis. This is essentially a laboratory diagnosis and there are no particular eatures which are diagnostic. However megaloblastic dyserythropoiesis e suspected in any anaemic patient who gives evidence of mulnutrition utrition, or who has disorders such as malaria and sickle-cell anaemia. ht diarrhoea and vomiting in infants with failure to thrive is often d when folic acid is added to the treatment. Megaloblastic anaemia is a n complication of pregnancy and may appear as early as twenty weeks n.

finding of a neurological disorder, particularly mental apathy and ral neuritis, and the presence of increased pigmentation of the palmar ould suggest vitamin B_{12} deficiency.

deficiency frequently co-exists with megaloblastic anaemia. Thus the blood appearances of oval macrocytic red cells well filled with haemo- may be modified by the presence of hypochromic and microcytic forms phic anaemia, p. **730**). The occurrence of hypersegmentation of the nuclei polymorph leucocytes is unfortunately not diagnostic of megaloblastic , as it may occur in iron deficiency states, but its presence should raise suspicions. Confirmation should be obtained, whenever possible, by the nation of a bone marrow aspirate. Bioassay of serum vitamin B_{12}, serum and red cell folate are very helpful if available.

tamin B_{12} deficiency is suspected, the presence of free hydrochloric acid in stric aspirate after administering pentagastrin will exclude Addisonian ious anaemia (p. **441**).

atment. Most cases will respond completely to folic acid (5 to 15 mg/day) uth. If vitamin B_{12} deficiency is considered likely it is wise to give hydroxo- amin by intramuscular injection (250 micrograms each week) until an ate dietary intake is assured. Where appropriate, iron should be given in the usual doses (p. **725**). In the majority of cases continued treatment is essary, but in pregnancy folic acid should be given until after delivery. If rhydria has been demonstrated and Addisonian pernicious anaemia is med or confirmed, it is necessary to continue treatment with hydroxo- amin throughout life. In remote areas or in other circumstances which regular injections impossible, a daily oral dose of 300 micrograms of cobalamin is a satisfactory, although probably inferior method of vitamin dministration.

vention. Because of the frequency of deficiency it is wise to add folic acid daily) to the treatment of all infants with kwashiorkor or other forms of itrition, with infections or with haemolytic anaemia. Similarly 350 micro- folic acid and 100 mg of elemental iron should be given daily from as early ssible throughout pregnancy.

HAEMOLYTIC ANAEMIA

The various types of haemolytic anaemia which occur in temperate are also encountered in tropical countries. Haemolytic anaemia in the t frequently due to malaria. In addition two types of genetic abnormality r in haemolytic anaemia are also particularly common, namely defici the enzyme glucose-6-phosphate dehydrogenase and the haemoglobino Haemolysis also occurs in acute bartonellosis (p. 16) and may be caused venom of certain snakes (p. 99).

Haemolytic Anaemia due to Malaria

An attack of malaria, especially when due to *Plasmodium falciparum*, is accompanied by haemolysis, and in a severe or prolonged attack very co able anaemia may ensue. The destruction of red cells in malaria is alw excess of that due to parasitised cells. The reason for this is ill-unde although it is most likely to be due to an immune mechanism. General degree of the anaemia is related to the severity of the parasitaemia. Dur acute attack of malaria the reticulocyte count may be low but as the p recovers a brisk outpouring of young red cells occurs. This recuperative re may be embarrassed by deficiency states, especially of folic acid and iron, other infections. Where these occur anaemia will be more severe and prol

A district can be classified as hypoendemic, mesoendemic, hyperende holoendemic according to the intensity of malarial transmission (p. **96** hyperendemic or holoendemic zones little anaemia is produced in the indig peoples over the age of 5 to 7 years, because of the development of a high of tolerance to the parasites ('premunity'). This tolerance is known to b judiced by the prolonged use of suppressive drugs or residence in malari areas, in pregnancy, following splenectomy and in diseases of the ret endothelial system such as lymphoma. Under these circumstances anaemi be seen in those previously immune. Anaemia occurs mostly in the non-im or weakly immune, such as visitors, young children and adults living in ar malarial hypoendemicity or mesoendemicity. In such patients splenomegal be a prominent feature. It follows from what has been said that in areas o endemicity treatment of malarial anaemia in the population is likely to be of transient benefit unless accompanied by eradication of the malaria. On the hand, in areas of high endemicity, unless eradication can effectively eliminat infection, there is a risk of creating an area of low endemicity with the sequent increase in malarial anaemia that would follow the inevitable dr individual immunity.

Anaemia resulting from haemolysis also occurs in blackwater fever (a co cation of neglected falciparum malaria [p. **966**]).

Glucose-6-phosphate Dehydrogenase Deficiency

Glucose-6-phosphate dehydrogenase is the first enzyme in the hexose phosphate shunt. Red cells derive most of their metabolic energy from glyc through the Embden-Meyerhof pathway but a fraction is used by the h osphate shunt whose function is to service the dependent glutathione ms employing the enzymes glutathione reductase and glutathione se. These enzymes protect the red cell against 'oxidant' damage. In the of G-6-PD this protective mechanism is crippled and certain 'oxidant' sufficient concentration can damage the red cell to the point that on occurs.

olytic anaemia following the ingestion of 8-aminoquinoline drugs has own to occur since 1926 when this effect was reported following the use quine. In 1945 it was appreciated that susceptibility occurred pre- tly in persons of Negro extraction and in 1952 that the effect was dose and could be produced by primaquine. It was not until 1956 that the ental abnormality, deficiency of glucose-6-phosphate dehydrogenase)) in the red cells of susceptible persons was elucidated.

now known that the deficiency is inherited as a sex-linked recessive and gh frequency among Negroes. In West and East Africa about 20 per cent s (hemizygotes) are affected, and about 4 per cent of females are homo- for the abnormal gene and are therefore also deficient. Many drugs in n clinical use, e.g. 8-aminoquinolines, antimalarials, sulphonamides, nes, nitrofurantoin, Naphthalene and vitamin K, are capable of pre- ng haemolysis in individuals with this defect. Infections may also have this nd may potentiate the haemolytic action of drugs and cause drugs such as licylic acid, ascorbic acid, chloramphenicol, chloroquine, mepacrine and etin to become harmful.

discovery that favism (haemolytic anaemia resulting from the ingestion of oad bean, *Vicia faba*) was due to deficiency of glucose-6-phosphate ogenase, indicated that this enzyme deficiency occurred also in inhabitants Mediterranean, Middle East and Far East. There are both electrophoretic antitative differences in activity between the enzyme in Negro and non- deficient patients. In Negroes the activity of the enzyme is about 15 per f that in non-deficient subjects whereas in the others it is often less than ent. Thus the clinical effects are greater in the non-Negro type of deficiency. tly some hitherto unexplained cases of haemolytic disease of the newborn lso been attributed to the same defect although in this respect the affected neonate is probably much less at risk. The water soluble synthetic in K analogues have been most frequently implicated. Yet other types of se-6-phosphate dehydrogenase biochemically different from the above may ociated with congenital nonspherocytic haemolytic disease and have been in persons of pure British ancestry. In these cases it is important to realise plenectomy is valueless.

sons with this enzyme deficiency normally enjoy good health, but are liable emolysis if any of the precipitating drugs or foods are injected or ingested. ver it must be emphasised that the haemolytic effect is dose related and will clinically detectable if the dose does not exceed a critical level. It is often le to employ doses which are not toxic. The anaemia when it occurs is in onset, usually becoming clinically obvious about 3 to 10 days after ure to the precipitating agent. There is evidence that the degree of haemo- ay be related to the dose of the agent. It may be sufficiently severe to cause globinuria as well as the other classical signs of haemolysis, namely

hyperbilirubinaemia of the unconjugated type, raised reticulocyte
nucleated red cells in the peripheral blood, absent haptoglobins and
malbuminaemia. In the Negro-type of deficiency only cells of a certain
over are involved, so that the haemolysis is to some extent self-limiti
when the offending drug is continued. Young red cells do have some gl
phosphate dehydrogenase activity, and remain viable until their enzyme
ment decays when they become susceptible to haemolysis. Since in the Ca
variety the enzyme activity of young cells is negligible the destruction
disastrous. Anuria is an infrequent but serious complication.

The diagnosis can be confirmed by estimating the enzyme activity of
cells. If anaemia is severe, transfusion of red cells with normal enzyme ac
necessary. More usually recovery occurs rapidly once the offending a
withdrawn or reduced in dose. As stated above, females may be homozyg
the gene resulting in glucose-6-phosphate dehydrogenase deficiency, they
homozygous for the allelomorphic normal gene or they may be hetero
Heterozygotes show enzyme level varying from normal to levels as low
found in deficient subjects. Those with very low levels suffer from hae
when provoked in the same way as deficient males and can be detected
simple screening tests. Heterozygotes with higher amounts of the enzyr
only be detected by direct assay methods and do not generally suffer
haemolysis even when provoked.

The survival of a harmful gene in high frequency can only be due to it c
ring an advantage to the heterozygote. As in the case of the sickling gene (
glucose-6-phosphate dehydrogenase deficiency is common only in areas
world where falciparum malaria was, at least until recently, endemic. But
evidence that deficiency of this enzyme protects against death from malaria
nearly so convincing as in the case of sickling. Whereas death from ce
malaria is exceptionally rare in heterozygotes for sickle-cell haemoglobin,
been reported in children with glucose-6-phosphate dehydrogenase defic
but not as frequently as in normal children in the same area.

THE HAEMOGLOBINOPATHIES

Sickle-cell Anaemia

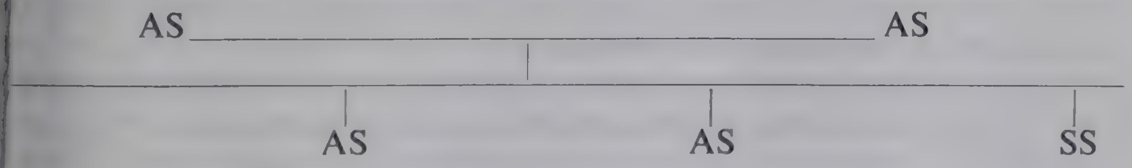
Sickle-cell anaemia has been recognised amongst Negroes and to a lesser e
amongst some inhabitants of the Mediterranean littoral since the beginni
the century. It is only comparatively recently, however, that it was found
due to the possession of the abnormal haemoglobin designated haemoglob

It is now known that abnormal haemoglobins result from amino acid subs
tions in their polypeptide chains. These in turn reflect mutations in the struc
genes controlling the production of these chains. There are four such struc
gene loci in humans, all on autosomal chromosomes and therefore paired.
are designated alpha (α), gamma (γ), beta (β) and delta (δ) and are respon
for the production of the three main haemoglobins seen during extra-uterine
namely haemoglobins F, A and A_2. Each of these haemoglobins contain
common two α chains, and their differences reflect the possession of two γ ch
in the case of haemoglobin F, two β chains in haemoglobin A and two δ chai

lobin A_2. Thus, the globin fraction of these three types of haemoglobin
written $\alpha_2\gamma_2$, $\alpha_2\beta_2$ and $\alpha_2\delta_2$ respectively. Each chain in the globin fraction
one haem moiety in its folds.

a chains possess 141 amino acids in sequence, and γ, β and δ chains 146.
acid substitutions may occur at any point along these chains. Each chain
'N' and a 'C' terminal and the polypeptide chains are numbered starting
e 'N' terminal. More than one kind of amino acid substitution can occur
point. For example the substitution of valine for glutamic acid at the N_6
n of the β chain produces haemoglobin S, whereas if the substitution is
aemoglobin C results. The beta chains of haemoglobin A are designated
d those of haemoglobin S and C, βS and βC respectively. Sickle cell
globin should be written $\alpha_2A\beta_2S$. However, it is convenient and practical
esent normal adult haemoglobin by the capital letter A and the abnormal
globins by S, C and E and so on. As there are now well over 200 haemo-
variants known, the letters of the alphabet do not suffice and for some
new variants have been given names, often of the towns or districts in
they were discovered. Sickle-cell haemoglobin is the most important, but
globins C, DPUNJAB and E are also important in the areas of the world
they occur, particularly when inherited together with haemoglobin S or
β-thalassaemia.

individual's haemoglobin is inherited from both parents. Thus, a normal
can be represented as having the haemoglobin genotype AA. Sickle-cell
s represented by AS and sickle-cell anaemia, or homozygous haemoglobin
ase, by SS. The inheritance when both parents have sickle-cell trait can be
ically shown thus:



ere is a high incidence of persons with sickle-cell haemoglobin in equatorial
a; in many countries, e.g. Nigeria and Uganda over 20 per cent of adults
the trait (i.e. Hb.AS) and in East Africa the incidence in some areas is as
as 40 per cent. About 9 per cent of American and West Indian Negroes have
rait. It is also found in inhabitants of some areas of North Africa, Greece,
hern Italy, the Middle East and Southern India. As most of the homo-
tes die before reaching puberty it is surprising that the genetic abnormality
ersisted. This has now been explained by the concept of balanced poly-
hism. By this is meant that the heterozygote (AS) must have a better chance
rviving than the normal homozygote (AA) to compensate for the increased
rate of the abnormal homozygotes (SS). It is now known that the hetero-
e is much less likely to die from falciparum malaria. This explains the high
ency of survival of the haemoglobin S gene in those areas of the world
e falciparum malaria is or was, until recently, endemic.

tients with sickle-cell anaemia do not, as might be imagined, have a greatly
ased resistance to falciparum malaria.

Clinical Features. An understanding of the pathology and symptomato sickle-cell anaemia must be based on a knowledge of the properties abnormal haemoglobin. When haemoglobin S is deoxygenated the molec haemoglobin polymerise to form pseudo-crystalline structures kno 'tactoids'. As these form they distort the red cell membrane and produ characteristic sickle shape of the cells. The polymerisation is reversible w oxygenation occurs. The distortion of the red cell membrane howeve become permanent and the cell 'irreversibly sickled'. The greater the conc tion of sickle-cell haemoglobin in the individual cell, the more easily 'ta are formed but this process may be enhanced or retarded by the prese other haemoglobins in the same cell. Thus haemoglobin C participates polymerisation more readily than haemoglobin A whereas haemoglo inhibits.

In homozygous S disease (sickle-cell anaemia) most of the red cells c haemoglobin S and little else and are very prone to 'sickle' even *in vivo* normal conditions. This happens particularly in those parts of the r vasculature where, for one reason or another, flow is sluggish. Sickled traverse capillaries poorly and tend to obstruct the flow thereby increasir sickling of other cells and causing cessation of flow. Thrombosis may follow an area of tissue infarction results associated with severe pain, swelling tenderness (pain crisis).

Sickled cells are phagocytosed in large numbers by the reticulo-endot system. This is reflected in hepatosplenomegaly which may be marked ea life. Repeated episodes of splenic infarction however, reduce the size of organ and if the patient survives to adult life the spleen may be impalpable. result of haemolysis the patient is usually jaundiced and this is further incre by the pathological changes in the liver. Occasionally, although surpris rarely, pigment gall-stones are formed.

There is a severe haemolytic disorder with a reduction in mean red cell life from 120 days to as little as 20 days and during crisis even less. The incre haemolysis is continuous and the haemoglobin level seldom rises above 100 ml and is usually in the order of 8 g/100 ml. Crises occur in which seque tion and destruction of the red cells is even further increased. During t periods the patient feels ill and feverish, becomes more jaundiced and the hae globin drops rapidly. The liver and spleen enlarge further. Such 'haemol crises' do not necessarily coincide with 'pain crises'. Aplastic crises simila those seen in other chronic haemolytic disorders have also been reported and usually associated with viral infections. This response to infection occur normal persons but a period of marrow inactivity passes unnoticed as the little drop in haemoglobin over one or two weeks. In patients with sickle anaemia the failure of red cell production can be a disaster; profound anaem inevitable and can be lethal.

The haemolytic anaemia developing in the first few months of life ca considerable marrow hyperplasia, expanding the marrow cavity and produ the bossed appearance of the skull, the protuberant teeth and prominent c bones. Radiological examination of the skull shows the 'hair on end' appear of the vault of the skull. The life-long haemolytic disease and anaemia w averages about 8 g/100 ml is associated with erythroid hyperplasia and incre s for folic acid. Megaloblastic change is a common complication in the ourished. Where folate deficiency has been long standing growth may be l, puberty delayed and the appearance mistaken for pituitary deficiency. ficiency is not common and a large amount of haemosiderin is usually liver, spleen and bone marrow. Chronic cardiomegaly is also common ttributed to the chronic severe anaemia.

rth the baby destined to have sickle-cell anaemia has no symptoms or the disease. The majority of the red cells carry haemoglobin F. As the over to cells carrying the 'adult' type of haemoglobin occurs symptoms ns appear; anaemia, jaundice and pain crises, the last classically in the and toes which show large fusiform swellings (dactylitis). The metacarpal tatarsal bones may also be involved. The late results seen in older children vious shortening of one or more digits.

ng infancy and childhood frequent attacks of painful swellings of the long and vertebrae may occur, due to infarction. These are characteristically in onset and often accompanied by increased jaundice. The pain is of everity as to confine the child to bed and, as fever is an invariable ac- niment, the episode may be mistaken for rheumatic fever. In any one e more than one bone may be affected. The attacks last 3 to 20 days and y subside gradually. There is often a fall in the haemoglobin level and this e sufficiently severe to require blood transfusion. The main complication to ared is osteomyelitis which is usually due to the *Salmonella* group of isms. The after effects of repeated infarction of bones can be demonstrated iographs of the diaphyseal areas. As the child grows older the frequency of -pain' crises becomes less, but periodic attacks are the rule throughout life. ler children and in adults superficial ulcers on the medial aspect of the leg, bove the ankle, are common and extremely slow to heal.

duced oxygen tension in the pulmonary circulation, due to respiratory tract ion or vascular occlusion with bone marrow emboli, leads to very rapid of severe dyspnoea, pulmonary hypertension and massive sequestration of d cells in the lungs. These pulmonary crises may be rapidly fatal. If ery occurs pulmonary fibrosis and cor pulmonale are common sequelae. ntravascular sickling occurs in the mesenteric vessels, the clinical features of en abdominal pain, vomiting, absent bowel sounds, board-like rigidity and closely simulate those of peritonitis or other abdominal emergency. uent diagnostic mistakes have been made and have led to death as a result of nnecessary laparotomy.

romboses in intracranial vessels will cause cerebral infarction. Since these cranial thromboses are usually venous, recovery is the rule, but focal psy may be a late sequel. Another not infrequent complication is painless aturia, due to infarction of the renal papillae.

gnosis. The diagnosis should always be suspected in a patient who has had toms of anaemia since infancy and who belongs to a race which may be ed with the sickle-cell trait. Enquiry will often reveal a history of episodes ne pain often referred to as 'rheumatism'. Microscopic examination of a d blood film from a patient with sickle-cell anaemia will show some sickle- d red cells but these will not be seen in the blood film from a person who has only the sickle-cell trait. The presence of haemoglobin S can be confir the demonstration that the red cells will sickle within 20 minutes when mix glass slide with a freshly prepared 2 per cent solution of sodium metabis and covered with a coverslip. Alternatively a small drop of blood dil saline may be incubated under a sealed coverslip overnight when sickli occur. A positive result will occur in the trait and in haemoglobin SC dis well as in sickle-cell anaemia.

When suspected, the diagnosis should always be confirmed by electrop analysis of the haemoglobin and, if necessary, by a family study to demo the inheritance. In this way true sickle-cell anaemia can be differentiate other diseases in which haemoglobin S is combined with thalassaemia o other abnormal haemoglobin such as C or D.

Treatment. There is no method of changing the genetic constitution individual and therefore no means of curing the disease. Intercurrent infec a particular hazard which can precipitate intravascular sickling. If proph or early treatment is given to prevent severe infections from developing, m health is avoided. When pregnancy occurs in a person with sickle-cell anae dangerous situation arises which is discussed below. In areas where mala endemic, children with sickle-cell anaemia should have constant antima prophylaxis, for although the presence of haemoglobin S in the red blood of those with the sickle-cell trait reduces the severity of falciparum mala does not altogether prevent it and the stress of even a mild infection m disastrous for the patient with sickle-cell anaemia. An adequate diet shou supplemented with folic acid 5 mg daily.

Attacks of bone pain should be treated with analgesics, such as cal acetylsalicylate, 1 g four-hourly or, if necessary, pethidine. The use of drugs are addictive should be avoided, if possible, since the repeated need for analg can be predicted. Dehydration, due to the inability of the kidney to concen the urine, must be avoided. A rapid intravenous infusion of sterile isotonic s (10 ml/kg body weight) may dramatically reduce pain in which case this infu may be repeated every 12 hours for a total of 48 hours, unless there is com relief sooner. If osteomyelitis is suspected a blood culture will help to identif responsible organism, which is usually one of the *Salmonella* group. Hence ei tetracycline, if the organism is sensitive to it, or chloramphenicol should be g immediately and continued for at least three weeks and until all signs of infec have resolved.

Blood transfusion is of temporary benefit only and should be reserved periods of particular risk, such as a fall in haemoglobin below 4 g per 100 or a severe infection. Transfusion itself is not without risk as the incidenc painful crises is related to increased blood viscosity, which is dependent on red cell count and the oxygen tension as well as on the amount of sickle- haemoglobin in each red cell. Haemolytic crises have also been seen to fo transfusion of compatible blood. Transfusion adds to the accumulation of which may in later life result in increased hazards due to siderosis. This da may be reduced by chelating agents (p. **959**). Furthermore the high incidenc viral infections in the tropics increases the risk of serum-transmitted hepa

ransfusion is considered necessary only blood of normal haemoglobin
uld be given.

ry is a particular hazard in sickle-cell anaemia. If even temporary and
noxia or venous congestion occurs intravascular sickling is very likely.
reason emergency operations should be avoided whenever possible and
uets must never be used. If operation is essential it should be carefully
so that adequate and continuous oxygenation is assured and the blood
e and limb temperature maintained at normal levels. In a severely ill
exchange transfusion with blood of normal haemoglobin type is ad-
. The immediate post-operative care should include frequent haemoglobin
inations and blood transfusion should be given if a sudden drop

nectomy is of value only in the very rare instance of a superadded hyper-
m.

gnosis. It is probable that in Africa, without medical attention, few children
ickle-cell anaemia survive to adult life. With full medical facilities many
survive as a result of the treatment described above and, although subject
ealth, lead a satisfying life.

Other Sickle-cell Diseases

e degree of anaemia and the frequency of crises depends upon the stability
particular combination of haemoglobin within individual red cells. Some
oglobins, e.g. haemoglobin DPUNJAB and haemoglobin C, co-operate with
-cell haemoglobin in the formation of tactoids and crises similar to those
in sickle-cell anaemia occur in persons who inherit one of these haemo-
ns with sickle-cell haemoglobin. The frequency and severity of these crises
ually less. Foetal haemoglobin co-operates poorly with sickle-cell haemo-
n and tends to prevent sickling. Thus persons who inherit the gene for
stence of foetal haemoglobin as well as sickle-cell haemoglobin may have no
cal disability because although each red cell contains 75 per cent haemo-
in S it also contains 25 per cent of the stabilising foetal haemoglobin.
n an individual inherits the gene for β-thalassaemia as well as the gene for
e-cell haemoglobin the result is haemoglobin-S-thalassaemia. This usually
es only moderate anaemia and mild, infrequent crises. In some cases, how-
the combination of sickle-cell haemoglobin and thalassaemia traits results
ises as severe as in sickle-cell anaemia and these patients are a considerable
sthetic risk.

aemoglobin C occurs almost exclusively in West Africans and their descend-
Because haemoglobin SC disease causes less disability than homozygous
e-cell anaemia, most patients survive into adult life. Pregnancy seems to be a
cular hazard, and in this disease aseptic necrosis of the femoral head, retinal
mbosis causing sudden deterioration in vision and painless haematuria are
uncommon complications. The treatment is the same as for sickle-cell
mia.

Pregnancy and Sickle-cell Disease

Relatively few patients with sickle-cell anaemia live long enough a
sufficiently fertile to conceive. Thus, although sickle-cell anaemia is more c
than haemoglobin SC disease, many more patients with the latter disor
seen in pregnancy. In the absence of careful supervision, both sickle-cell a
and haemoglobin SC disease carry a high morbidity and mortality
pregnancy. There are three complications which should be particularly

The first is megaloblastic dyserythropoiesis and anaemia due to deficie
folic acid. This reflects the high demand for folic acid occasioned by t
existence of a chronic severe haemolytic disorder with pregnancy. Both
are capable of inducing folic acid deficiency; together they almost always

The second is an increased incidence of severe sequestration (haem
crises associated with rapid enlargement of the spleen and liver and a r
dropping haemoglobin level. These tend to occur towards the end of preg
and in the puerperium and require urgent treatment with transfusion.

The third and sometimes the most hazardous is the development of
infarcts. When this happens towards the end of pregnancy, fat and bone m
embolism often occurs and may produce blockage of the pulmonary vascul
acute pulmonary hypertension and death. Proteinuria may appear an
patient's deterioration be attributed wrongly to pre-eclamptic toxaemia.
mistake can be lethal. The treatment consists of heparinisation and, if nece
the premature induction of labour or delivery by Caesarean section. Seda
are contra-indicated. Heparinisation is discontinued in the second stage of la
and restarted within four hours of the termination of labour and continue
three to four days. Heparin is administered preferably by continuous i
venous infusion and the dose adjusted to give a prothrombin time between
and four times that of a control sample.

These patients need very careful antenatal and postnatal care. They mu
given folic acid (5 mg daily) throughout pregnancy. Arrangements shoul
made for delivery in hospital and for the patient to live sufficiently close for e
admission should a crisis develop during the last trimester. During a bone
crisis very careful and frequent clinical examination and haemoglobin determ
tion should be made. Exchange blood transfusion may be necessary if there
sudden fall in haemoglobin either before delivery or in the puerperium.

Sickle-cell Trait

This is generally a harmless condition but in conditions resulting in abnorm
lowered oxygen tension of the blood, intravascular sickling can occur in a pe
with the sickle-cell trait and the clinical picture of a sickle-cell crisis res
These conditions are encountered at altitudes above 15,000 feet, and thus in
flying in unpressurised aircraft. Another potential hazard is anaesthesia
severe anoxia. Bloodless field surgery can be disastrous.

Even in the absence of a generalised reduced oxygen tension it is claimed
persons with the sickle-cell trait are liable to attacks of haematuria du
infarction of renal papillae and also that they are more likely to develop o
myelitis due to the *Salmonella* group of organisms than are persons with no

lobin. Nevertheless, as has been mentioned above, there is good evidence sons with the sickle-cell trait have an advantage over those with normal lobin in that they are less likely to die from falciparum malaria. Persons kle-cell trait have a reduced ability to concentrate urine although the s not as severe as that in sickle-cell anaemia.

nosis. The finding of a positive sickling test in association with a normal ance of the blood film is presumptive of the sickle-cell trait. The diagnosis confirmed by electrophoresis of a haemolysate.

Other Abnormal Haemoglobin Diseases

other abnormal haemoglobins are less important, but both haemoglobin haemoglobin E, when inherited in the homozygous state, result in a mild of haemolytic anaemia. In others, although haemolysis occurs, it is ately compensated for by increased erythropoiesis. The mechanism under- he haemolysis is not yet clear. Haemoglobin DPUNJAB and haemoglobin E special importance if inherited together with β-thalassaemia. The result is a lytic anaemia with laboratory and clinical features intermediate in severity en those of thalassaemia major and minor.

THALASSAEMIA

alassaemia is an inherited disorder of haemoglobin synthesis, in which there tial or complete failure to synthesise the polypeptide chains of the haemo- n molecule. The exact nature of the defect is not yet understood. Beta chain esis is most commonly affected. When the abnormality is inherited from one it only (heterozygote) synthesis of haemoglobin is only mildly affected and disability occurs. When the patient is homozygous synthesis is grossly ired and severe anaemia results.

ilure to synthesise beta (β) chains (β-thalassaemia) is the commonest type is seen in highest frequency in the peoples of the Mediterranean littoral. rozygotes have what has been called thalassaemia minor, a condition in h there is usually mild anaemia and little or no clinical disability. Homo- tes (thalassaemia major) are unable to synthesise haemoglobin A and, after neonatal period, have a profound hypochromic anaemia associated with h evidence of red cell dysplasia and increased red cell destruction. In these ents there is no inhibition of delta (δ) chain production and this is optimally to give relatively high levels of haemoglobin A_2 ($\alpha_2\delta_2$) (p. 129). Haemo- in F ($\alpha_2\gamma_2$) production is normally switched off in the neonatal period, but use of the severe anaemia some production persists and HbF may provide h of the circulating haemoglobin. Thus these patients attempt to supply requirements with haemoglobins that normally comprise only 3 per cent e total. At best they usually manage little more than 30 to 50 per cent of ormal adult complement of haemoglobin.

e anaemia is crippling and the possibility of survival for more than a few s without transfusion is poor. Bone marrow hyperplasia early in life may produce head bossing, prominent malar eminences and other changes giving mongoloid appearance. The skull X-ray shows a 'hair on end' appearance an general widening of medullary spaces which may interfere with the developme of the paranasal sinuses. Development and growth is retarded and folic aci deficiency may occur. Splenomegaly is an early and prominent feature. Hepato megaly is slower to develop but may become massive especially if splenectomy i undertaken. Transfusion therapy inevitably gives rise to haemosiderosis. Cardia enlargement is common and cardiac failure in which siderosis may play a part is frequent terminal event.

Diagnosis. Thalassaemia minor is often detected only when iron therapy for a mild hypochromic anaemia fails. The demonstration of microcytes, increase resistance of red cells to osmotic lysis and a raised haemoglobin A_2 fraction together with evidence of the same abnormalities in other members of the family establishes the diagnosis. In contrast haemoglobin A_2 levels are diminished in iron deficiency states.

The diagnosis of thalassaemia major is made by the finding of profound hypochromic anaemia associated with evidence of severe red cell dysplasia, erythroblastosis, and the absence or gross reduction of the amount of haemoglobin A, raised levels of haemoglobin F and evidence that both parents have thalassaemia minor.

It is not within the scope of this book to detail the great variation in the severity of the clinical manifestations of thalassaemia that present a spectrum of disease severity rather than two syndromes. It is clear that there are several types of β-thalassaemia but for further study the reader is referred to publications dealing with this subject in greater detail.

Treatment. Transfusion is the mainstay in the treatment of homozygous β-thalassaemia. Nevertheless, it is important to realise that transfusions are not required unless the haemoglobin falls significantly below 7 g/100 ml, unless a definite commitment to a transfusion life is undertaken, in which case the haemoglobin level should be maintained between 10 and 12 g/100 ml. At this level the benefit from transfusion is optimal and the transfusion requirements minimal. The intraperitoneal route may be used in the young to conserve veins. Iron therapy is strongly contraindicated but folic acid supplements are advisable. Attempts to remove iron by the administration of chelating agents may be employed, but at best such therapy fails to keep pace with the iron deposition that results from transfusion therapy (250 mg of elemental iron in every 500 ml of whole blood). Splenectomy may be required for mechanical reasons or if it can be shown to be a site of major red cell destruction. Intercurrent infection must be treated vigorously with appropriate antibiotics.

Alpha Thalassaemia. Alpha thalassaemia is found mainly in South-East Asia. There are probably at least two inherited abnormalities, one associated with severe, and the other with mild inhibition of alpha (α) chain production. Heterozygotes of either abnormality are at little disadvantage since α-chain production is adequate. A slight excess of gamma chain production at birth may form tetramers (γ_4), (haemoglobin Bart's) and this can be demonstrated by electrophoretic techniques. The combination of a mild and a severe α-thalassaemia der results in a deficiency of α chain production which is short of absolute, at some normal haemoglobin is formed. There is an excess of beta chains these form tetramers (β_4), (haemoglobin H) and this may explain the syn-ne of haemoglobin H disease. The inheritance of the severe α-thalassaemia ormality from both parents is incompatible with life and such offspring are born (hydrops foetalis).

iagnosis. Heterozygotes for α-thalassaemia can be diagnosed with certainty at birth when a raised level of haemoglobin Bart's is found. This disappears he production of γ chains is switched off. Thereafter α chain production ears to be adequate and few if any β tetramers (haemoglobin H) form. A d degree of microcytosis and hypochromia may be present.

atients with haemoglobin H disease have hypochromic, microcytic anaemia n decreased osmotic fragility and reticulocytosis and classically show multiple usions in the red cells when these are incubated with Brilliant Cresyl Blue. In lition haemoglobin H may be demonstrated in a freshly prepared haemolysate electrophoresis.

The diagnosis of homozygous α-thalassaemia is suggested by the finding of a found anaemia in a stillborn hydropic baby. Some haemoglobin Bart's may demonstrable and evidence of heterozygosity in both parents.

Treatment. Most patients with this disorder are asymptomatic. Patients with emoglobin H disease require management in the same way as patients with thalassaemia.

SPLENOMEGALY AND ANAEMIA

A striking feature of medical practice in the tropics is the frequency with hich splenic enlargement, sometimes to an extreme degree, is encountered in ssociation with some degree of anaemia. Whereas such presentation in the emperate areas of the world would suggest leukaemia or reticulosis, the more ommon causes in the tropics are malaria (p. **965**), visceral leishmaniasis (p. 2), hronic brucellosis (p. 78), schistosomiasis (p. 64), haemoglobinopathies (p. 130) nd cirrhosis of the liver (p. **558**).

In some cases it is not possible to attribute the illness to any of these causes, nd the terms idiopathic or cryptogenic have been used of the splenomegaly. There is evidence that this splenomegaly is an abnormal reaction to chronic nalarial infection. Far from being typical cases of clinical malaria these patients ave no fever, and malarial parasites are more difficult to demonstrate in their lood than in the general population. They show evidence, however, of a hyper-mmune state; there is a characteristic infiltration of the sinusoids in the liver and one marrow with mature lymphocytes, and a higher level of malarial antibodies n their serum than in the serum of the general population. It is probably also ignificant that these patients often respond to long-term malarial prophylaxis nd this is the treatment of choice. In many cases the splenomegaly reduces onsiderably or even disappears altogether. Cessation of therapy results in a eappearance of the disorder, and prophylaxis should be maintained for life. In some cases, splenectomy may appear indicated and considerable improvemen the anaemia and the patient's well-being may accrue. However, it must be bo in mind that splenectomy in such patients may be associated with a grea increased susceptibility to malarial infection thereafter, if life-long prophylaxi not included in their treatment.

Accompanying gross splenomegaly, whatever the cause, there is usua anaemia attributable to the haemodilution associated with an enlarged sple and this is mainly due to an increase in plasma volume. The reason for th increase is not understood. In addition, some degree of hypersplenism, chara terised by haemolysis, thrombocytopenia and leucopenia, frequently is prese (p. **756**).

It should be noted that this idiopathic type of splenomegaly may complica disorders also associated with splenomegaly. Thus patients with chronic lymphat leukaemia may present with enormous splenomegaly and this splenomegaly an the associated anaemia may be greatly improved by long-term malarial prophylaxis.

ONYALAI

The name 'onyalai' has been given to a form of thrombocytopenic purpura of unknown origin which occurs sporadically in various parts of Africa. It differs from essential thrombocytopenia in that it affects mainly young male adults, is not prone to relapses and large haemorrhagic bullae on the tongue and buccal mucosa are a conspicuous feature. Haemorrhages from the gastric mucosa, the renal tract and elsewhere may cause death from anaemia. Haemorrhages into the brain may also be fatal. Anaemia should be corrected by blood transfusions and iron medication. In some cases corticosteroids have been reported as being effective in controlling the thrombocytopenia.

N. C. ALLAN.

ex

dex

e numbers in bold type refer to items included in *Davidson's Principles and Practice of licine*, 11th edition, and which are omitted from this Supplement.

A

climatisation to heat, 114
kee poisoning, 113
tinomycetecea, 91
.der, 98
des aegypti, 41, 44
rican lymphoma, 109
rican River Blindness, 82
lescheria boydii, 91
pha-thalassaemia, 135
mastigotes, 2
moebiasis, **970**
mphotericin B, 7, 90
naemia, haemolytic. *See* Haemolytic anaemia
  in the tropics, 124
  megaloblastic, 124
  sickle-cell. *See* Sickle-cell anaemia
ncylostoma, braziliense, 75
ncylostoma caninum, 75
  duodenale, 71
ncylostomiasis, 71
  anaemia due to, 72, 124
  clinical features, 72
  treatment, 73
Anthrax, 27
Antimonials, pentavalent, in leishmaniasis, 3, 5, 7
    in rhinosporidosis, 95
  trivalent, in reactions in leprosy, 23
    in Schistosomiasis, 66
Antivenom, 100
Aphiochaeta, 98
Arboviruses, classification, 40
Argemone mexicana, 112
Argemone poisoning, 112
Argentine haemorrhagic fever, 48
Armillifer, armillatus, 96
  moniliformis, 96
Arsenobenzyl sulphate, 11
Ascariasis, **979**
Ascites, chylous, 78
Asthenia, tropical anhidrotic, 116
Athlete's foot, 88
Atrax robustus, 101
Auchmeromyia luteola, 97
Australorbis, 67

B

Bacillary dysentery, **74**
Bacillus anthracis, 27
Bacteria, diseases due to, 15
Balantidiasis, 12
Balantidium coli, 12
Bantu siderosis, 106
Bartonella bacilliformis, 15
Bartonellosis, 15
BAY b 5097, 92
Bay sore, 6
B.C.G. vaccination in leprosy, 23
Bee stings, 102
Bejel, 35
Bephenium hydroxynaphthoate, 73
Beriberi, **153**
Beta-thalassaemia, 135
Bilharziasis. *See* Schistosomiasis
Biomphalaria, 67
Bite, spider, 101
Bithionol, 69
Blackwater fever, 126, **966**
Blastomyces, brasiliensis, 93
  dermatitidis, 93
Blastomycoses, 93
Blighia sapida, 113
Bolivian haemorrhagic fever, 48
Borrelia, duttoni, 36
  recurrentis, 36
  vincenti, 107
Boxfish, 104
Brill's disease, 54
Brucellosis, **79**
  cirrhosis of liver in, 107
Brugia, filariasis, 79
  malayi, 79
  pahangi, 79, 84
Bubonic plague, 29
Bug, reduviid, 10
Bulinus, 67
Burkitt's lymphoma, 109
Buruli ulcer, 108

C

Calabar swellings, 80
Calliphora, 97

Callitrogra hominiovorax, 97
Cancrum oris, 109
Capillaria philippinensis, 123
Carcinoma, from tropical ulcer, 107
Cardiomyopathy, tropical, **287**
Carrión's disease, 15
Cephalosporium falciforme, 91
Cerastes cornutus, 100
Chagas' disease, 10
Chancre, trypanosomal, 8
Chancroid, 32
Chicleros ulcer, 6
Chigoe flea, 96
Chikungunya virus, 41, 45
Chironex fleckeri, 103
Chiropsalmus quadrigatus, 103
Chlamydia, 50
Cholera, 24
  treatment, 25
Chorio-retinitis, in toxoplasmosis, 13
Chromoblastomycosis, 93
Chrysomyia bezziana, 97
Chrysops, 80, 81
Chylous ascites, 78
Chyluria, 78
Cladosporium, 93
Climatic bubo, 50
Clofazimine, 23
Clonorchiasis, 67
Clonorchis sinensis, 67
Cobra, 98
Coccidioides immitis, 94
Coccidioidomycosis, 94
Colubridae, 98
Cone shells, 103
Conidae, 103
Cooley's anaemia. *See* Thalassaemia
Cordylobia anthropophaga, 97
Co-trimoxazole, 90, 92, 93
Councilman bodies, 42
  burneti, 58
Crotalaria, 105
Crotalidae, 99
Cryptococcosis, 94
Cryptococcus neoformans, 94
Culex fatigens, 76
Culicoides, austeni, 84
  grahami, 84
Cyclophosphamide, 110
Cyclops, 75, 86
Cysticercosis, **983**

D

Dactylitis, in sickle-cell anaemia, 130
  in yaws, 33
Dapsone, 21, 92
Dasyatidae, 104
DDS, 21
Dengue, 44
Dermatobia hominis, 97
Dermatophytosis, 88
Diamino-diphenyl-sulphone, 21
Diarrhoea, flagellate, 12
Dichuchwa, 35
Diethylcarbamazine, 76, 79, 83, 86
Dimercaprol (B.A.L.), 9
Diodontidae, 104
Dipetalonema, perstans, 83, 84
  streptocerca, 83
Diphyllobothrium, latum, **978, 1135**
  mansoni, 105
Diptera, 97
Dirofilaria immitis, 79, 84
Donovan bodies, 15
Donovanosis, 15
Dracontiasis, 86
Dracunculus medinensis, 86
Dropsy, epidemic, 112
Dye test, for toxoplasmosis, 14
Dysentery, amoebic, **970**
  bacillary, **74**

E

Elapidae, 98
Elephantiasis, 78
Encephalitis, Japanese B, 47
Endemic haemoptysis, 68
Enhydrina schistosa, 98
Enteric fevers, **69**
Enterobiasis, **978**
Eosinophilia, tropical pulmonary, 84
Epidemic dropsy, 112
Epidermophyton, 88
Ephithelioma, from tropical ulcer, 107
Epstein-Barr virus, 109
Erythema nodosum leprosum, 20
Espundia, 6
Exhaustion, heat, 116

F

Faget's sign, 42
Fannia, 97
Fasciola hepatica, 69
Fascioliasis, 69
Fasciolopsiasis, 70
Fasciolopsis buski, 70
Favism, 127
Favus, 89
Fever, blackwater, 126, **966**
  enteric, **69**
  haemorrhagic, with renal syndrome, 48
  Haverhill, 38

—*continued*
a, 48
ya, 15
botomus, 45
ite, 38
psing, louse-borne, 36
ck-borne, 37
ky Mountain spotted, 55
dfly, 45
ch, 59
low, 41
asis, 76
ugia, 79
uchereria, 76
poisonous, 104
ellate diarrhoea, 12
orocytosine, 94
rouracil, 114
nboesia, 32
test, 51
gi, diseases due to, 88
azolidine, 25
iformis fusiformis, 107
obacterium fusiforme, 107

G

ngosa, 34
ardia intestinalis, 12
ardiasis, 12
ossina, morsitans, 7
pallidipes, 7
palpalis, 7
swynnertoni, 7
tachinoides, 7
lucose-6-phosphate dehydrogenase deficiency, 126
nathostoma spinigerum, 75
oundou, 33
ranuloma venereum, 15
riseofulvin, 89
roin, hanging, 82
uerreiro-Machado reaction, 11
uinea worm infection, 86

H

aemaphysalis, 46
aemoglobin, abnormal, 128
Barts, 137
DPUNJAB, 129
H, 137
SC disease, 133
S-thalassaemia, 133
aemoglobinopathies, 128
aemolytic anaemia, and blackwater fever, 126

Haemolytic anaemia—*continued*
and glucose-6-phosphate dehydrogenase deficiency, 126
and malaria, 126
and Oroya fever, 16
and snake bite, 99
Haemophilus ducreyi, 32
Haemoptysis, endemic, 68
Haemorrhagic fever, with renal syndrome, 48
Halberstaedter-Prowazek bodies, 52
Halzoun, 96
Hanging groin, 82
Haverhill fever, 38
Heat, acclimatisation to, 114
effects of, 113
prevention of ill-effects from, 118
prickly, 115
Heat exhaustion, 116
Heat hyperpyrexia, 117
Heat syncope, 115
Helminthic infections, 61, 973
Hexachloroparaxylol, 68
Histoplasma, capsulatum, 89
duboisii, 90
Histoplasmosis, 89
Hookworm infection. *See* Ancylostomiasis
Hycanthone, 66
Hydrophidae, 98
2-hydroxystilbamidine, 93
Hyperpyrexia, heat, 117
Hypersplenism, 138
Hypoderma bovis, 97

I

Irukandji stings, 103

J

Japanese B encephalitis, 47
Jellyfish stings, 103
Jigger flea, 96

K

Kala azar, 2
Katayama syndrome, 62
Kaposi's sarcoma, 110
Keratosis, solar, 114
Klebsiella granulomatis, 15
Krait, 98
Kuru, 49
Kyasanur Forest disease, 46

L

Larva, currens, 74
  migrans, 75
Lassa fever, 48
Laticauda colubrina, 98
Latrodectus, indistinctus, 101
  mactans, 101
Leishman-Donovan (L.D.) bodies, 2
Leishmania, americana, 6
  braziliensis, 6
  donovani, 2
  mexicana, 6
  peruviana, 6
  tropica, 4
Leishmaniases, 2
Leishmaniasis, cutaneous, 4
  diffuse cutaneous, 5
  recidiva, 5
  South American, 6
  visceral, 2
Leprosy, 17
  clinical features, 19
  diagnosis, 21
  pathology, 18
  reactions in, 20
  treatment, 21
Leptospirosis, **82**
Leptotrombidium (leptotrombidium), akamushi, deliense, 56
Levamisole, 73
Light, effects of, 113
Linguatula serrata, 96
Liver, cirrhosis of, Indian childhood, 106
  fibrosis of, 105
    and iron, 106
  veno-occlusive disease of, 105
Loa loa, 80
Loiasis, 80
Lucilia, 97
Lygranum antigen, 51
Lymphogranuloma inguinale, 50
Lymphoma, African, 109
  Burkitt's, 109
Lymphopathia venereum, 50

M

Madura foot, 91
Madurella, grisea, 91
  mycetomi, 91
Maduromycetoma, 92
Malaria, **964**
  anaemia due to, 126
  and splenomegaly, 137
  fibrosis in, 107
Mamba, 98
Mangroves, 79
Mansonella ozzardi, 84
Mansonioides, 80
Megaloblastic anaemia, 124
  in sickle-cell anaemia, 131
Megaselia, 98
Melarsonyl potassium, 10
Melarsoprol, 9
Melioidosis, 17
Mepacrine, in giardiasis, 13
Metronidazole, 13
Microfilariae, 77
Microsporum, 88
Montenegro test, 6
Mossy foot, 93
Mycetoma, 91
Mycobacterium leprae, 17
Mycobacterium ulcerans, 109
Mycoses, superficial, 88
Mycotic infections, 88
Myelo-optico neuropathy, 113
Myiasis, 97
  aural, 98
  cutaneous, 97
  intestinal, 97
  ocular, 98
  of wounds, sores and cavities, 97
Myositis, tropical, 104

N

Necator americanus, 71
Neuropathy, subacute myelo-optico, 113
Niridazole, 87
  in schistosomiasis, 66
Nitrofurazone, 10
Njovera, 35
Nocardia, asteroides, 91
  brasiliensis, 91
  caviae, 91
Nocardiosis, 91
Nutritional disorders, **112**

O

Octopus bites, 102
Oestrus ovis, 98
Onchocerca volvulus, 81
Onchocerciasis, 81
Oncomelania, 67
Onyalai, 138
Opisthoglypha, 98
Oriental sore, 4
Ornithodorus, moubata, 38
  tholozani, 38
Oroya fever, 15
Orthomerphalan, 110
Ostraciontidae, 104

P

occidioidomycosis, 93
onimiasis, 68
gonimus westermani, 68
gra, **158**
amidine isethionate, 4, 9
lophora, 91
lophora jeanselmei, 91
bitis, tropical, 104
botomus fever, 45
botomus, noguchi, 16
apatasii, 45
errucarum, 16
salia, 103
ta, 35
viper, 99
yrosporum orbiculare, 88
yriasis versicolor, 88
gue, 29
bubonic, 29
pneumonic, 30
septicaemic, 29
anorbarius, 67
anorbis boissyi, 65
neumonic plague, 30
rocephalosis, 96
regnancy, and sickle-cell disease, 134
rickly heat, 115
roteroglypha, 98
Pseudomonas, mallei, 20
  pseudomallei, 17
Psittacosis, **346**
Pyomyositis, 104
Pyrimethamine, and sulphonamide in toxoplasmosis, 14
  in South American leishmaniasis, 7

Q

Q fever, 57

R

Rabies, **972**
Ragwort, 105
Rat-bite fevers, 38
Rattlesnake, 99
Relapsing fever, louse-borne, 36
  tick-borne, 37
Rhinosporidiosis, 95
Rhinosporidium seeberii, 95
Rickettsia, akari, 58
  australis, 56
  conori, 56
  conori pijperi, 56
  mooseri, 53
  prowazeki, 53
Rickettsia—continued
  quintana, 59
  rickettsi, 55
  tsutsugamushi, 56
Rickettsial diseases, 53
  treatment and prophylaxis, 59
Rickettsialpox, 58
Rifampicin, 22
Ringworm, 88
Rocky Mountain spotted fever, 55
Romana's sign, 11
Russell viper, 98

S

Salines, isotonic, in treatment of cholera, 26
Salmonella, in sickle-cell anaemia, 131
Salmonelloses, **71**
Sandflies, in bartonellosis, 15
  in leishmaniasis, 2
  in sandfly fever, 45
Sandfly fever, 45
Sarcoma, Kaposi's, 110
  of skin, idiopathic multiple haemorrhagic, 110
Sarcophaga, 97
Schistosoma, bovis, 61
  haematobium, 61, 62
  intercalatum, 61
  japonicum, 61, 64
  mansoni, 61, 63
  mattheei, 61
Schistosomiasis, 61
  diagnosis, 65
  treatment, 66
Scorpion stings, 102
Scrapie, 50
Screw worm, 97
Scrub typhus, 56
Senecio, 105
Septicaemic plague, 29
Setaria cervi, 79
Sibbens, 35
Sickle-cell anaemia, 128
  clinical features, 130
  fibrosis of liver in, 107
  treatment, 132
Sickle-cell disease, and pregnancy, 134
Sickle-cell trait, 134
Sickling test, 131
Siderosis, Bantu, 106
Simulium, bovis, 81
  damnosum, 81
  neavei, 81
Siti, 35
Sivvens, 35
Skerljevo, 35
Sleeping sickness, 7

Smallpox, **89**
Snake bite, 98
  classification, 98
  clinical features, 99
  treatment, 100
Sodium antimonyl tartrate, 66
Sodium stibogluconate, 3
Sodoku, 38
Soft sore, 32
Solar keratosis, 114
Solenoglypha, 99
Spider bite, 107
Spirilla, diseases due to, 38
Spirillum minus, 38
Spirochaetes, diseases due to, 33
Splenomegaly, and anaemia, 137
  cryptogenic, 137
  idiopathic, 138
Sporotrichosis, 93
Sporotrichum schenckii, 93
Sprue, tropical, 119
Stibocaptate, 66
Stingrays, 104
Stings, bee, 102
  Irukandji, 103
  jellyfish, 103
  of fish, 103
  scorpion, 102
Streptobacillus moniliformis, 38
Streptomyces, madurae, 91
  pelletieri, 91
  somaliensis, 91
Strongyloides stercoralis, 74
Strongyloidiasis, 74
Subacute myelo-optico neuropathy, 113
Sulfoxine, 22
Sunburn, 113
Suramin, 83
Syphilis, endemic (non-venereal), 35
Synanceja trachynis, 103
Syncope, heat, 115

T

Taeniasis, **981**
Tetanus, **76**
Tetrachloroethylene, 71, 73
Tetraodontidae, 104
Thalassaemia, major, 135
  minor, 135
Thiabendazole, 75
Thiambutosine, 22
Threadworms, **978**
Ticks, 37, 40, 46, 55
Tinaderm, 88
Tinea, capitis, 88
  corporis, 88
  cruris, 88
Tinea—*continued*
  unguium, 88
  versicolor, 88
Tityus trinitatis, 102
Tolnaftate, 88
Torres inclusion body, 42
Torulosis, 94
Toxocara, canis, 75
  cati, 76
Toxoplasma gondii, 13
Toxoplasmosis, 13
Trachoma, 51
Tree snake, 98
Trench fever, 59
Treponema, carateum, 35
  pallidum, 35
  pertenue, 33
Triaziquone, 111
TRIC agent, 51
Trichinosis, **980**
Trichophyton, 88
Trichophyton schoenleinii, 89
Trichuris trichiura, **980**
Trombicula, akamushi, 56
  deliensis, 56
Tropical anhidrotic asthenia, 116
Tropical myositis, 104
Tropical phlebitis, 104
Tropical pulmonary eosinophilia, 84
Tropical sprue, 119
Tropical ulcer, 107
Tropicorbis, 67
Trypanosoma, brucei, 7
  congolense, 7
  cruzi, 10
  equiperdum, 8
  gambiense, 7
  rhodesiense, 7
  vivax, 7
Trypanosomiasis, African, 7
  American, 10
Tsetse flies, 7
Tularaemia, 31
Tunga penetrans, 96
Typhus endemic, 54
  epidemic, 54
  scrub, 56
Typhus fever, flea-borne, 55
  louse-borne, 54
  mite-borne, 56
  tick-borne, 55

U

Ulcer, Buruli, 108
  tropical, 107
Ulcerating granuloma of the pudenda, 15
Uta, 6

V

occlusive disease of liver, 105
ga peruana, 15
o, *cholerae*, 24
or, 24
a berus, 100
idae, 98
iting sickness of Jamaica, 113

W

er hyacinths, 79
l-Felix reaction, 54
pworms, **980**
tfield's ointment, 88
hlfahrtia magnifica, 97
ol-sorter's disease, 27
Wuchereria bancrofti, 76
Wuchereria filariasis, 76

X

Xenodiagnosis, 11
Xenopsylla, *astia*, 55
  cheopis, 55
  spp., 29

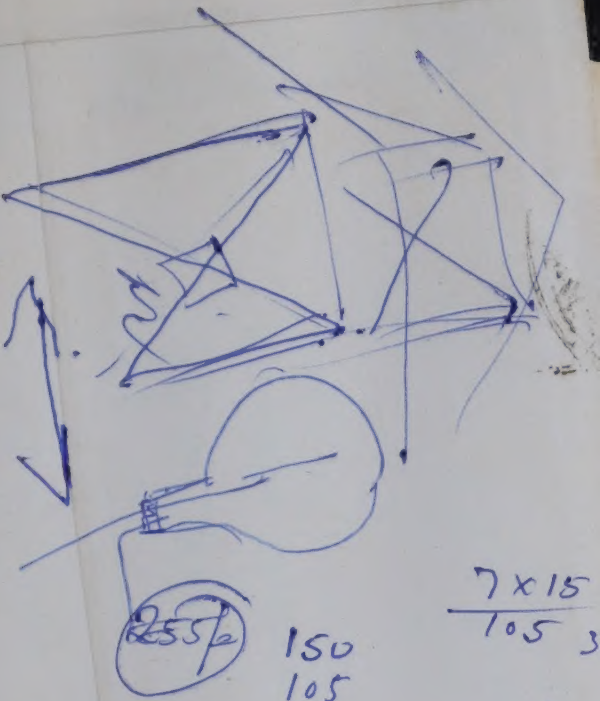
Y

Yaws, 32
Yellow fever, 41
Yersinia, *pestis*, 29
  tularensis, 31

Printed by T. & A. Constable Ltd., Edinburgh

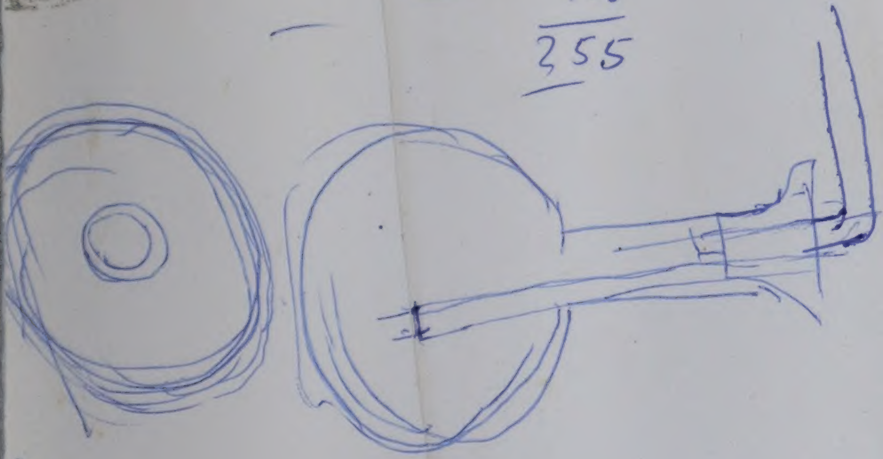
[illegible]

J.R.L.



7 x 15
105 3

150
105
255



Ro.50x3
1.50